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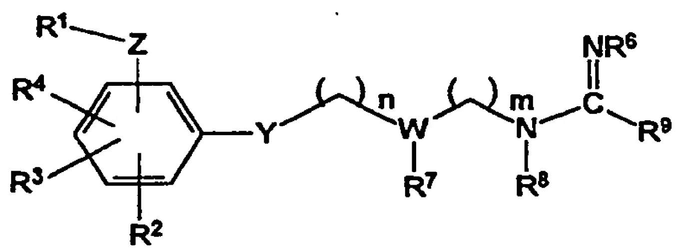
(54) Title: AMIDINO PROTEASE INHIBITORS

(57) Abstract

Amidino and benzamidino compounds, including compounds of Formula (I), wherein R^1-R^4, R^6-R^9, Y, Z, n and m are set forth in the specification, as well as hydrates, solvates or pharmaceutically acceptable salts thereof, that inhibit a number of proteolytic enzymes are described. Also described are methods for preparing the compounds of Formula (I).



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Amidino Protease Inhibitors

Background of the Invention

Field of the Invention

The present invention relates to novel compounds that function as enzyme inhibitors, and particularly to a new class of non-peptidic inhibitors of proteolytic enzymes.

Related Art

Proteases are enzymes that cleave proteins at single, specific peptide bonds. Proteases can be classified into four generic classes: serine, thiol or cysteinyl, acid or aspartyl, and metalloproteases (Cuypers *et al., J. Biol. Chem. 257*:7086 (1982)). Proteases are essential to a variety of biological activities, such as digestion, formation and dissolution of blood clots, reproduction and the immune reaction to foreign cells and organisms. Aberrant proteolysis is associated with a number of disease states in man and other mammals. The human neutrophil proteases, elastase and cathepsin G, have been implicated as contributing to disease states marked by tissue destruction. These disease states include emphysema, rheumatoid arthritis, corneal ulcers and glomerular nephritis. (Barret, in *Enzyme Inhibitors as Drugs*, Sandler, ed., University Park Press, Baltimore, (1980)). Additional proteases such as plasmin, C-1 esterase, C-3 convertase, urokinase, plasminogen activator, acrosin, and kallikreins play key roles in normal biological functions of mammals. In many instances, it is beneficial to disrupt the function of one or more proteolytic enzymes in the course of therapeutically treating a mammal.

Serine proteases include such enzymes as elastase (human leukocyte), cathepsin G, plasmin, C-1 esterase, C-3 convertase, urokinase, plasminogen activator, acrosin, chymotrypsin, trypsin, thrombin, factor Xa and kallikreins.

Human leukocyte elastase is released by polymorphonuclear leukocytes at sites of inflammation and thus is a contributing cause for a number of disease states. Cathepsin G is another human neutrophil serine protease. Compounds with the ability to inhibit the activity of these enzymes are expected to have an anti-inflammatory effect useful in the treatment of gout, rheumatoid arthritis and other inflammatory diseases, and in the treatment of emphysema. Chymotrypsin and trypsin are digestive enzymes. Inhibitors of these enzymes are useful in treating pancreatitis. Inhibitors of urokinase and plasminogen activator are useful in treating excessive cell growth disease states, such as benign prostatic hypertrophy, prostatic carcinoma and psoriasis.

The serine protease thrombin occupies a central role in hemostasis and thrombosis, and as a multifactorial protein, induces a number of effects on platelets, endothelial cells, smooth muscle cells, leukocytes, the heart, and neurons (Tapparelli *et al.*, *Trends in Pharmacological Sciences 14*:366-376 (1993); Lefkovits and Topol, *Circulation 90*(3):1522-1536 (1994); Harker, *Blood Coagulation and Fibrinolysis 5 (Suppl 1)*:S47-S58 (1994)). Activation of the coagulation cascade through either the intrinsic pathway (contact activation) or the extrinsic pathway (activation by exposure of plasma to a non-endothelial surface, damage to vessel walls or tissue factor release) leads to a series of biochemical events that converge on thrombin. Thrombin cleaves fibrinogen ultimately leading to a hemostatic plug (clot formation), potently activates platelets through a unique proteolytic cleavage of the cell surface thrombin receptor (Coughlin, *Seminars in Hematology 31*(4):270-277 (1994)), and autoamplifies its own production through a feedback mechanism. Thus, inhibitors of thrombin function have therapeutic potential in a host of cardiovascular and non-cardiovascular diseases, including: myocardial infarction; unstable angina; stroke; restenosis; deep vein thrombosis; disseminated intravascular coagulation caused by trauma, sepsis or tumor metastasis; hemodialysis; cardiopulmonary bypass surgery; adult respiratory distress syndrome; endotoxic shock; rheumatoid

arthritis; ulcerative colitis; induration; metastasis; hypercoagulability during chemotherapy; Alzheimer's disease; and Down's syndrome.

Factor Xa is another serine protease in the coagulation pathway. Factor Xa associates with factor Va and calcium on a phospholipid membrane thereby forming a prothrombinase complex. This prothrombinase complex then converts prothrombin to thrombin (Claeson, *Blood Coagulation and Fibrinolysis 5*:411-436 (1994); Harker, *Blood Coagulation and Fibrinolysis 5 (Suppl 1)*:S47-S58 (1994)). Inhibitors of factor Xa are thought to offer an advantage over agents that directly inhibit thrombin since direct thrombin inhibitors still permit significant new thrombin generation (Lefkovits and Topol, *Circulation 90*(3):1522-1536 (1994); Harker, *Blood Coagulation and Fibrinolysis 5 (Suppl 1)*:S47-S58 (1994)).

A need continues to exist for non-peptidic compounds that are potent and selective protease inhibitors, and which possess greater bioavailability and fewer side-effects than currently available protease inhibitors. Accordingly, new classes of potent protease inhibitors, characterized by potent inhibitory capacity and low mammalian toxicity, are potentially valuable therapeutic agents for a variety of conditions, including treatment of a number of mammalian proteolytic disease states.

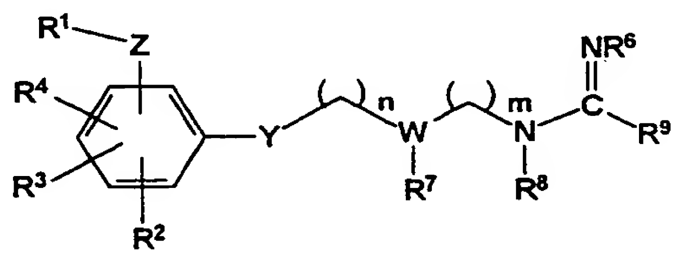
Summary of the Invention

The present invention is directed to novel compounds having one of Formulae ***I-III*** (below). Also provided are processes for preparing compounds of Formulae ***I-III***. The novel compounds of the present invention are potent inhibitors of proteases, especially trypsin-like serine proteases, such as chymotrypsin, trypsin, thrombin, plasmin and factor Xa. Certain of the compounds exhibit antithrombotic activity via direct inhibition of thrombin, or are intermediates useful for forming compounds having antithrombotic activity. Other compounds are inhibitors of trypsin and/or chymotrypsin, and are therefore useful in treating pancreatitis. Also provided are methods of inhibiting or treating

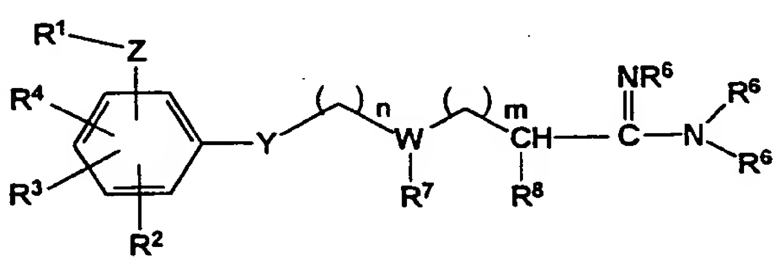
aberrant proteolysis in a mammal and methods of treating thrombosis, ischemia, stroke, restenosis or inflammation in a mammal by administering an effective amount of a compound of Formulae ***I-III***. Further provided are pharmaceutical compositions comprising a compound of Formulae ***I-III*** and one or more pharmaceutically acceptable carriers or diluents.

Detailed Description of the Preferred Embodiments

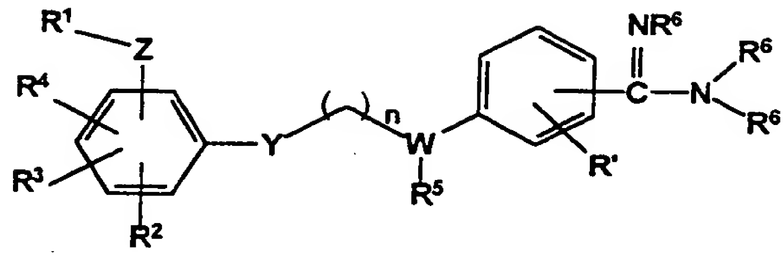
Compounds of the present invention include compounds having one of Formulae ***I-III***:



I



II



III

or solvates, hydrates or pharmaceutically acceptable salts thereof;

wherein:

Z is one of $-NR^{10}SO_2-$, $-SO_2NR^{10}-$, $-NR^{10}C(R^yR^z)-$, $-C(R^yR^z)NR^{10}-$, $-OSO_2-$, $-SO_2O-$, $-OC(R^yR^z)-$, $-C(R^yR^z)O-$, $-NR^{10}CO-$ or $-CONR^{10}-$;

R^y and R^z are each independently one of hydrogen, alkyl, cycloalkyl, aryl, aralkyl, hydroxyalkyl, carboxyalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl or carboxy;

R^1 is one of alkyl, cycloalkyl, alkenyl, alkynyl, aryl, aralkyl or heteroaryl, any of which may be optionally substituted;

R^2, R^3 and R^4 are each independently one of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, aralkyl, heteroaryl, trifluoromethyl, halogen, hydroxyalkyl, cyano, nitro, carboxamide, $-CO_2R^x$, $-CH_2OR^x$ or $-OR^x$, or when present on adjacent carbon atoms, R^2 and R^3 may also be taken together to form one of $-CH=CH-CH=CH-$ or $-(CH_2)_q-$, where q is from 2 to 6, and R^4 is defined as above;

R^x, in each instance, is independently one of hydrogen, alkyl or cycloalkyl wherein said alkyl or cycloalkyl groups may optionally have one or more unsaturations;

Y is one of $-O-$, $-NR^{10}-$, $-S-$, $-CHR^{10}-$ or a covalent bond;

W is N or CR^{10};

R^5 is one of hydrogen, alkyl, aralkyl, aryl, hydroxyalkyl or carboxyalkyl;

R^6, in each instance, is independently one of hydrogen, alkyl, hydroxy, alkoxy, aryloxy, aralkoxy, alkoxycarbonyloxy, cyano or $-CO_2R^w$, where R^w is alkyl or cycloalkyl;

R^7 and R^8 are each independently one of hydrogen, alkyl, aralkyl, aryl, hydroxyalkyl or carboxyalkyl, or R^7 and R^8 are taken together to form $-(CH_2)_y-$, where y is zero, 1 or 2, with the proviso that when W is N, y cannot be zero or 1;

R^9 is one of hydrogen, alkyl, cycloalkyl or aryl, wherein said alkyl, cycloalkyl or aryl can be optionally substituted with amino, monoalkylamino, dialkylamino, alkoxy, hydroxy, carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, aryl, heteroaryl, acylamino, cyano or trifluoromethyl;

R^{10}, in each instance, is independently one of hydrogen, alkyl, aralkyl, aryl, hydroxyalkyl, aminoalkyl, monoalkylamino(C_{2-10})alkyl, dialkylamino (C_{2-10})alkyl or carboxyalkyl;

R' is one of hydrogen, alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, trifluoromethyl, halogen, hydroxyalkyl, cyano, nitro, carboxamide, carboxy, alkoxycarbonyl or alkoxyalkyl;

n is from zero to 8, with the proviso that when W is N and Y is other than $-CHR^{10}-$, then n is from 2 to 8; and

m is from 1 to 4, provided that when W is N, then m is not 1.

A preferred group of compounds falling within the scope of the present invention include compounds of Formulae ***I-III*** wherein:

Z is one of $-SO_2O-$, $-SO_2NR^{10}-$, $-C(R^yR^z)O-$ or $-OC(R^yR^z)-$, where R^y and R^z are each hydrogen;

R^1 is one of C_{6-10} aryl, pyridinyl, quinizolinyl, quinolinyl or tetrahydroquinolinyl, any of which is optionally substituted by one or two of hydroxy, nitro, trifluoromethyl, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} aminoalkyl, C_{1-6} aminoalkoxy, amino, mono(C_{1-4})alkylamino, di(C_{1-4})alkylamino, C_{2-6} alkoxycarbonylamino, C_{2-6} alkoxycarbonyl, carboxy, C_{1-6} hydroxyalkyl, C_{2-6} hydroxyalkoxy, C_{2-10} mono(carboxyalkyl)amino, di(C_{2-10} carboxyalkyl)amino, C_{6-14} ar(C_{1-6}) alkoxycarbonyl, C_{2-6} alkynylcarbonyl, C_{1-6} alkylsulfonyl, C_{2-6} alkenylsulfonyl, C_{2-6} alkynylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonamido, amidino, guanidino, C_{1-6} alkyliminoamino, formyliminoamino, C_{2-6} carboxyalkoxy,

C_{2-6} carboxyalkyl, carboxyalkylamino, cyano, trifluoromethoxy, and perfluoroethoxy;

R^2, R^3 and R^4 are independently one of hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, phenyl, benzyl, trifluoromethyl, halogen, hydroxy(C_{1-8})alkyl, cyano, nitro, carboxamide, carboxy, C_{1-4} alkoxycarbonyl, C_{1-4}alkoxymethyl or C_{1-4} alkoxy; or alternatively, R^2 and R^3, when present on adjacent carbon atoms, may also be taken together to form one of –CH=CH–CH=CH– or $-(CH_2)_q-$, where q is from 2 to 6, and R^4 is as defined above;

Y is one of –O–, –S–, $-NR^{10}-$, or a covalent bond;

W is N or CR^{10};

R^5 is one of hydrogen, C_{1-4} alkyl, C_{2-10} carboxyalkyl or C_{2-10} hydroxyalkyl;

R^6, in each instance, is one of hydrogen, C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy, phenoxy, C_{1-4} alkyloxycarbonyl or cyano;

R^7 and R^8 are independently one of hydrogen, C_{1-6} alkyl, C_{2-10} carboxyalkyl or C_{2-10} hydroxyalkyl, or R^7 and R^8 are taken together to form $-(CH_2)_y-$ where y is 0, 1 or 2, provided that when W is N, y cannot be 0 or 1;

R^9 is hydrogen; or C_{1-10} alkyl, optionally substituted with amino, mono(C_{1-4})alkylamino, C_{1-6} alkoxy, hydroxy, carboxy, phenyl, alkyloxycarbonyl, aralkoxycarbonyl, C_{1-6} acylamino, cyano or trifluoromethyl;

R^{10}, in each instance, is independently hydrogen, C_{1-6} alkyl, benzyl, phenyl, C_{2-10} hydroxyalkyl, C_{2-10} aminoalkyl, C_{1-4} monoalkylamino(C_{2-8})alkyl, C_{1-4} dialkylamino(C_{2-8})alkyl or C_{2-10} carboxyalkyl;

R' is one of hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, phenyl, benzyl, trifluoromethyl, halogen, hydroxy(C_{1-8})alkyl, cyano, nitro, carboxamide, carboxy, alkoxycarbonyl, alkoxymethyl or alkoxy;

n is from zero to 8, with the proviso that when W is N, then n is from 2 to 8; and

m is from 1 to 4, provided that when W is N, then m is not 1.

An especially preferred group of compounds include compounds of Formulae *I-III* wherein:

Z is one of $-SO_2O-$, $-SO_2NR^{10}-$, $-CH_2O-$ or $-OCH_2-$;

R^1 is one of phenyl or naphthyl, optionally substituted by one or two of chloro or dimethylamino;

R^2 and R^3 are each hydrogen or R^2 and R^3 may also be taken together to form $-CH=CH-CH=CH-$;

R^4 is one of hydrogen, methyl, methoxy or trifluoromethyl;

Y is one of O or NR^{10};

W is N or CR^{10};

R^5 is one of hydrogen, C_{1-6} alkyl, C_{2-10} hydroxyalkyl or C_{2-10} carboxyalkyl;

R^6, in each instance is hydrogen or hydroxy;

R^7 and R^8 are independently one of hydrogen, C_{1-6} alkyl, C_{2-10} hydroxyalkyl or C_{2-10} carboxyalkyl, or R^7 and R^8 are taken together to form $-(CH_2)_y-$, where y is zero, 1 or 2, with the proviso that when W is N, y cannot be zero or 1;

R^9 is hydrogen or C_{1-4} alkyl;

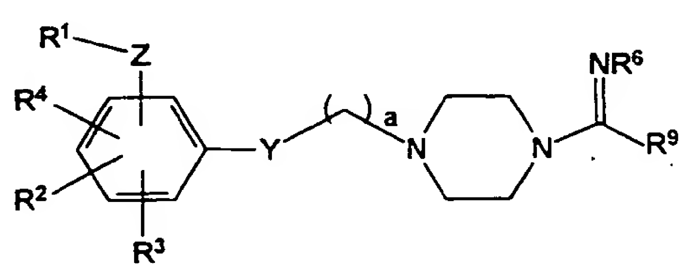
R^{10}, in each instance, is independently hydrogen, C_{1-4} alkyl, C_{2-4} hydroxyalkyl, C_{2-4} carboxyalkyl, C_{2-4} aminoalkyl, dimethylamino(C_{2-8})alkyl, methylamino(C_{2-8})alkyl;

R' is hydrogen, methyl, methoxy or trifluoromethyl;

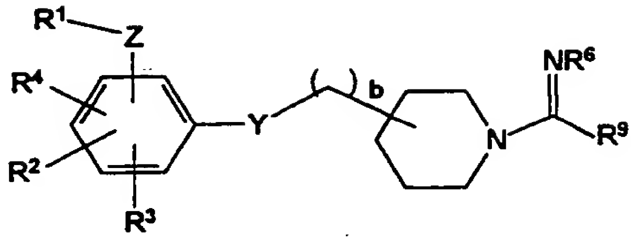
n is from zero to 4, with the proviso that when W is N, then n is 2 to 4; and

m is 1, 2 or 3.

Useful compounds falling within the scope of Formula *I* include compounds having one of Formulae *IV-VI*:

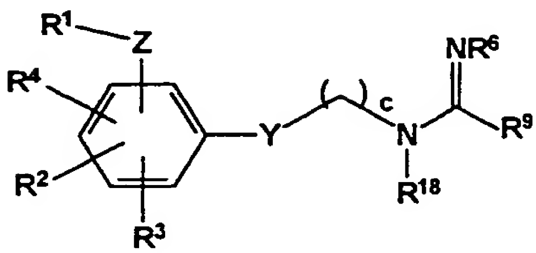


IV



V

and



VI

or solvates, hydrates or pharmaceutically acceptable salts thereof;

wherein:

Z, R^1, R^2, R^3, R^4, Y, R^6, R^9 and R^{10} are defined as above for Formulae *I-III*;

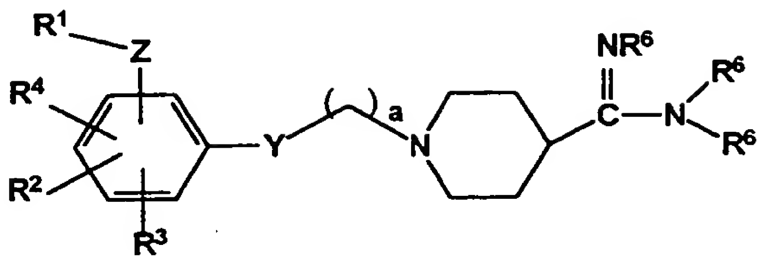
R^{18} is one of hydrogen, alkyl, aralkyl, aryl, C_{2-10} hydroxyalkyl or C_{2-10} carboxyalkyl;

a is from 1 to 8, provided that when Y is other than $-CHR^{10}-$, then a is from 2 to 8;

b is from 1 to 8; and

c is from 1 to 13, provided that when Y is other than $-CHR^{10}-$, then c is from 2-13.

Preferred compounds falling within the scope of Formula *II* include compounds having one of Formulae *VII-IX*:



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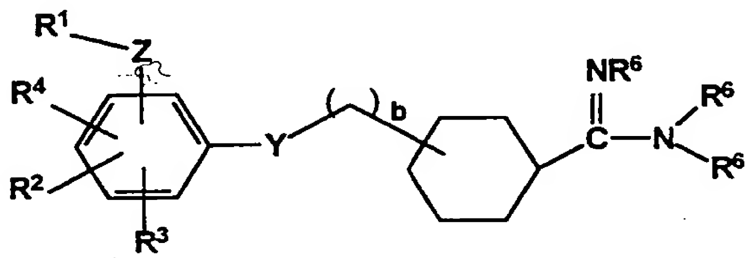
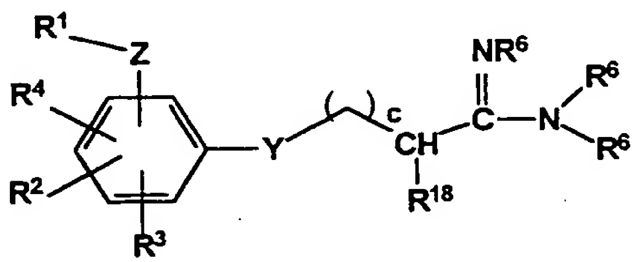


VIII



IX

or solvates, hydrates or pharmaceutically acceptable salts thereof;

wherein:

Z, R^1, R^2, R^3, R^4, Y, R^6, R^9 and R^{10} are defined as above for Formulae *I-III*;

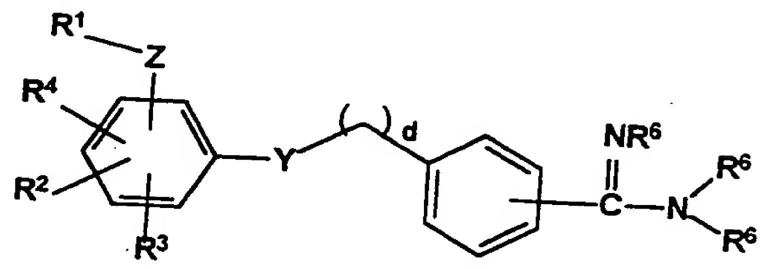
R^{18} is one of hydrogen, alkyl, aralkyl, aryl, C_{2-10} hydroxyalkyl or C_{2-10} carboxyalkyl;

a is from 1 to 8, provided that when Y is other than $-CHR^{10}-$, then a is from 2 to 8;

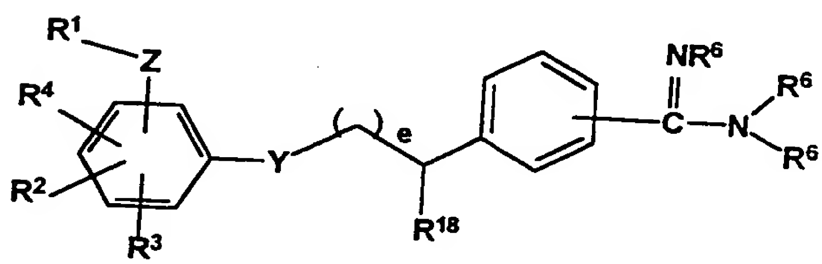
b is from 1 to 8; and

c is from 1 to 13, provided that when Y is other than $-CHR^{10}-$, then c is from 2-13.

Preferred compounds falling within the scope of Formula *III* include compounds having one of Formulae *X* or *XI*:



X



XI

or solvates, hydrates or pharmaceutically acceptable salts thereof;

wherein:

Z, R^1, R^2, R^3, R^4, Y, R^6, R^9 and R^{10} are defined as above for Formulae *I-III*;

R^{18} is one of alkyl, aralkyl, aryl, C_{2-10} hydroxyalkyl or C_{2-10} carboxyalkyl;

d is from 1 to 8; and

e is from 1 to 8.

The moiety $-Z-R^1$ of Formulae *I-XI* is attached to the benzene ring in a position *ortho-*, *meta-* or *para-* to Y.

The amidino moiety ($-C(=NR^6)NR^6R^6$) of Formulae *III*, *X* and *XI* can be attached in the *ortho-*, *meta-* or *para-* positions.

Preferred compounds of the present invention are those of Formula *I-XI* wherein Y is one of divalent oxygen (—O—) or $—NR^{10}—$ and Z is one of $—SO_2NR^{10}—$, $—SO_2O—$ or $—CH_2O—$.

Preferred compounds of the present invention are those of Formula ***I-XI*** wherein R^1 is one of C_{1-12} alkyl, C_{4-7} cycloalkyl, C_{2-8} alkenyl, C_{2-8} alkynyl or C_{6-14} aryl, especially C_{6-10} aryl, any of which is optionally substituted. Substituents that can be optionally present on the R^1 moieties include one or more, preferably one or two, hydroxy, nitro, trifluoromethyl, halogen, alkoxy, aminoalkoxy, aminoalkyl, hydroxyalkyl, hydroxyalkoxy, cyano, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl, carboxyalkoxy, mono(hydroxyalkyl)amino, di(hydroxyalkyl)amino, mono(carboxyalkyl)amino, di(carboxyalkyl)amino, alkoxycarbonylamino, alkoxycarbonyl, aralkoxycarbonyl, alkenylcarbonyl, alkynylcarbonyl, alkylsulfonyl, alkenylsulfonyl, alkynylsulfonyl, alkylsulfinyl, alkylsulfonamido, amidino, guanidino, alkyliminoamino, formyliminoamino, trifluoromethoxy or perfluoroethoxy. A further substituent on aryl, cycloalkyl, alkenyl, alkynyl and aralkyl moities of R^1 includes one or more, preferably one or two, alkyl moieties. Preferred values of optional substituents on R^1 include hydroxy, nitro, trifluoromethyl, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} aminoalkyl, C_{1-6} aminoalkoxy, amino, mono(C_{1-4})alkylamino, di(C_{1-4})alkylamino, C_{2-6} alkoxycarbonylamino, C_{2-6} alkoxycarbonyl, carboxy, C_{1-6} hydroxyalkyl, C_{2-10} mono(carboxyalkyl)amino, di(C_{2-10} carboxyalkyl)amino, C_{6-14} ar(C_{1-6} alkoxycarbonyl, C_{2-6} alkynylcarbonyl, C_{1-6} alkylsulfonyl, C_{2-6} alkenylsulfonyl, C_{2-6} alkynylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonamido, amidino, guanidino, C_{1-6} alkyliminoamino, formyliminoamino, C_{2-6} carboxyalkoxy, carboxyalkylamino, cyano, trifluoromethoxy, and perfluoroethoxy.

An additional preferred group of compounds are those compounds of Formulae ***I-XI*** wherein R^1 is heteroaryl or substituted heteroaryl. Preferred R^1 heteroaryl groups include pyridyl, thienyl, chromenyl, benzoxazolyl, quinazolinyl, quinolinyl and tetrahydroquinolinyl, with pyridyl, quinazolinyl, quinolinyl and tetrahydroquinolinyl being most preferred. Preferred compounds when R^1 is substituted heteroaryl include those compounds having one of the heteroaryl groups mentioned as preferred that have one or more, preferably one or two, substituents that are listed in the preceding paragraph.

Useful values of R^1 include phenyl, chlorophenyl, iodophenyl, dichlorophenyl, bromophenyl, trifluoromethylphenyl, di(trifluoromethyl)phenyl, methylphenyl, *t*-butylphenyl, methoxyphenyl, dimethoxyphenyl, hydroxyphenyl, carboxyphenyl, aminophenyl, methylaminophenyl, *n*-butylaminophenyl, amidinophenyl, guanidinophenyl, formyliminoaminophenyl, acetimidoylaminophenyl, methoxycarbonylphenyl, ethoxycarbonylphenyl, carboxymethoxyphenyl, naphthyl, hydroxynaphthyl, cyclohexyl, cyclopentyl, 2-propylbutyl, quinolinyl and tetrahydroquinolinyl.

The groups R^2, R^3 and R^4 in Formulae *I-XI* substitute for any remaining hydrogen atoms on the benzene ring after allowing for attachment of the moiety $-Z-R^1$. Preferred compounds are those where R^2, R^3 and R^4 are independently hydrogen, C_{1-4} alkyl, C_{4-7} cycloalkyl, C_{6-14} aryl, especially C_{6-10} aryl, C_{6-10} ar(C_{1-4})alkyl, trifluoromethyl, halogen, hydroxyalkyl, cyano, nitro, carboxamide, carboxy, alkoxycarbonyl, carboxymethyl, alkoxycarbonylmethyl, or cycloalkyloxycarbonyl. Alternatively, R^2 and R^3, when attached to adjacent carbon atoms on the benzene ring, are one of —CH=CH—CH=CH— or —$(CH_2)_q$—, where q is from 2 to 6, thereby forming a fused ring. Preferred values of R^2 together with R^3 include —CH=CH—CH=CH—, —CH_2—CH_2—CH_2— and —CH_2—CH_2—CH_2—CH_2—. When R^2 and R^3 together form a fused ring, R^4 is preferably hydrogen.

Useful values of R^2, R^3 and R^4 include hydrogen, methyl, ethyl, chloro, bromo, trifluoromethyl, hydroxymethyl, methoxy, ethoxy, carboxamide, nitro, phenyl, cyclopropyl, hydroxy, isopropyl, methoxycarbonyl, ethoxycarbonyl and benzyl. Useful values of R^2, R^3 and R^4 also include R^2 and R^3 together forming –CH=CH–CH=CH or –CH_2–CH_2–CH_2– and R^4 being hydrogen.

Preferred values of R^6 in Formulae *I-XI* are hydrogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, cyano or $-CO_2R^w$, where R^w, in each instance, is preferably one of C_{1-4}alkyl or C_{4-7}cycloalkyl. Suitable values of R^6 include hydrogen, methyl, ethyl, propyl, *n*-butyl, hydroxy, methoxy, ethoxy, cyano, $-CO_2CH_3$, $-CO_2CH_2CH_3$ and $-CO_2CH_2CH_2CH_3$. In the most preferred embodiments, each R^6 is hydrogen.

Preferred compounds include compounds of Formulae *I* and *II*, where R^7 and R^8 are independently one of hydrogen, C_{1-6} alkyl, C_{6-10} ar(C_{1-6})alkyl, C_{6-10} aryl, C_{2-10} hydroxyalkyl or C_{2-7} carboxyalkyl, or R^7 and R^8 are taken together to form $-(CH_2)_y-$, where y is most preferably 2. Useful values of R^7 and R^8 include hydrogen, methyl, ethyl, propyl, *n*-butyl, benzyl, phenylethyl, 2-hydroxyethyl, 3-hydroxypropyl, 4-hydroxybutyl, 2-carboxymethyl, 3-carboxyethyl and 4-carboxypropyl.

Preferred compounds are those of Formulae *I*, *IV*, *V* and *VI*, wherein R^9 is C_{1-10} hydrogen or alkyl optionally substituted by one, two or three of, preferably one of, amino, monoalkylamino, dialkylamino, alkoxy, hydroxy, alkoxycarbonyl, aryloxycarbonly, aralkoxycarbonyl, carboalkoxy, phenyl, cyano, trifluoromethyl, acetylamino, pyridyl, thienyl, furyl, pyrrolyl or imidazolyl.

Suitable values of R^9 include hydrogen, methyl, ethyl, propyl, *n*-butyl, benzyl, phenethyl, 2-hydroxyethyl, 3-hydroxypropyl, 4-hydroxybutyl, carboxymethyl and carboxyethyl.

Preferred values of R^{10} in Formulae *I-XI* include hydrogen, C_{1-6} alkyl, C_{6-10} ar(C_{1-6})alkyl, C_{6-10} aryl, C_{2-10} hydroxyalkyl C_{2-10} aminoalkyl, C_{2-7} carboxyalkyl, mono(C_{1-4} alkyl)amino(C_{1-8})alkyl, and di(C_{1-4} alkyl)amino (C_{1-8})alkyl. Suitable values of R^{10} include methyl, ethyl, propyl, *n*-butyl, benzyl, phenylethyl, 2-hydroxyethyl, 3-hydroxypropyl, 4-hydroxybutyl, 2-aminoethyl, 2-carboxymethyl, 3-carboxyethyl, 4-carboxypropyl and 2-(dimethylamino)ethyl.

Preferred values of n in Formulae *I-III* include from 1 to 6, more preferably from 1 to 4, and most preferably 1 or 2, with the proviso that when W is N and Y is other than $-CHR^{10}-$, then n is not 1. Preferred values of m include from 1 to 4, more preferably 1, 2 or 3, provided that when W is N, then m is not 1.

Preferred values of R^5 in Formula *III* include is one of hydrogen, C_{1-4} alkyl, phenyl, benzyl, phenethyl, C_{2-10} carboxyalkyl and C_{2-10} hydroxyalkyl. Especially preferred values are hydrogen, C_{1-6} alkyl, C_{2-10} hydroxyalkyl and C_{2-10}

carboxyalkyl. Suitable values of R^5 include hydrogen, methyl, hydroxymethyl, hydroxyethyl, carboxymethyl and carboxyethyl.

Preferred values of R' in Formula *III* include hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, phenyl, benzyl, trifluoromethyl, halogen, hydroxy(C_{1-8})alkyl, cyano, nitro, carboxamide, carboxy, alkoxycarbonyl, alkoxymethyl and alkoxy. Suitable values of R' include hydrogen, methyl, methoxy and trifluoromethyl;

Preferred values of "a" in Formulae *IV* and *VII* include from 1 to 6, more preferably from 1 to 4, and most preferably 1 or 2, with the proviso that when Y is other than $-CHR^{10}-$, then n is not 1.

Preferred values of "b" in Formulae *V* and *VIII* include from 1 to 6, preferably from 1 to 4, and most preferably 1 or 2.

Preferred values of "c" in Formulae *VI* and *IX* include from 1 to 8, more preferably from 1 to 6, and most preferably 1, 2, 3, or 4.

Preferred values of "d" and "e" in Fromulae *V* and *XI* include from 1 to 6, preferably from 1 to 4, and most preferably 1 or 2.

Preferred compounds of Formulae *VI, IX* and *XI* are those where R^{18} is independently one of hydrogen, C_{1-6} alkyl, C_{6-10} ar(C_{1-6})alkyl, C_{6-10} aryl, C_{2-10} hydroxyalkyl and C_{2-7} carboxyalkyl. Useful values of R^{18} include hydrogen, methyl, ethyl, propyl, *n*-butyl, benzyl, phenylethyl, 2-hydroxyethyl, 3-hydroxypropyl, 4-hydroxybutyl, 2-carboxymethyl, 3-carboxyethyl and 4-carboxypropyl. Most preferred compounds are those where R^{18} is hydrogen.

Specific compounds within the scope of the invention include the following examples:

2-chlorobenzenesulfonic acid 3-[(1-acetimidoylpiperidin-4-yl)methoxy]-5-methylphenyl ester hydrochloride;

3-(2-chlorobenzyloxy)-5-methyl-1-[2-(1-acetimidoyl)piperazin-4-yl]]ethoxybenzene diacetic acid salt;

N-[2-(N,N-dimethylamino)ethyl]-N-[2-[[4-(1-acetimidoyl)amino]butoxy]-4-methylphenyl]benzenesulfonamide dihydrochloride;

N-benzyl-N-[[[3-(1-acetimidoyl)piperidin-4-yl]methylamino]phenyl]-benzenesulfonamide;

3-chlorobenzenesulfonic acid 3-[[(1-acetimidoyl)piperidin-4-yl]methoxy]-5-methylphenyl ester hydrochloride;

2-chlorobenzenesulfonic acid 3-[(3-amidinophenyl)methoxy]-5-methylphenyl ester hydrochloride;

2-chlorobenzenesulfonic acid 3-[[3-(N-hydroxy)amidinophenyl]methoxy]-5-methylphenyl ester hydrochloride;

2,3-dichlorobenzenesulfonic acid 3-[[(1-acetimidoyl)piperidin-4-yl]methoxy]-5-methylphenyl ester hydrochloride;

2-chloro-N-[[3-[(1-acetimidoyl)piperidin-4-yl]methoxy]-5-trifluoromethylphenyl]benzenesulfonamide hydrochloride;

2-chloro-N-(5-carboxypentyl)-N-[[3-[(1-acetimidoyl)piperidin-4-yl]methoxy]-5-trifluoromethylphenyl]benzenesulfonamide;

1-(5-(N,N-dimethylamino)naphthalenesulfonic acid 3-[[(1-acetimidoyl)piperidin-3-yl]methoxy]-5-methoxyphenyl ester hydrochloride;

2-chlorobenzenesulfonic acid 1-[[(1-acetimidoyl)piperidin-4-yl]methoxy]naphthalen-3-yl ester acetic acid salt;

3-[(2-chlorophenoxy)methyl]-[[(1-acetimidoyl)piperidin-4-yl]methoxy]benzene acetic acid salt;

2-Chlorobenzenesulfonic acid 3-[(4-amidinophenyl)methoxy]-5-methylphenyl ester hydrochloride;

2-chlorobenzenesulfonic acid 3-[(3-amidinophenyl)methoxy]phenyl ester hydrochloride;

2-chlorobenzenesulfonic acid 3-[5-amidinopentyloxy]-5-methylphenyl ester acetic acid salt;

2-chlorobenzenesulfonic acid 3-[3-amidinopropoxy]-5-methylphenyl ester hydrochloride; and

2-chlorobenzenesulfonic acid 3-[[3-(N-methylamidino)phenyl]methoxy]-5-methylphenyl ester hydrochloride.

It is also to be understood that the present invention is considered to include stereoisomers as well as optical isomers, e.g. mixtures of enantiomers as well as individual enantiomers and diastereomers, which arise as a consequence of structural asymmetry in selected compounds of the present series.

The compounds of Formulae *I-XI* may also be solvated, especially hydrated. Hydration may occur during manufacturing of the compounds or compositions comprising the compounds, or the hydration may occur over time due to the hygroscopic nature of the compounds.

The term "aryl" as employed herein by itself or as part of another group refers to monocyclic or bicyclic aromatic groups containing from 6 to 12 carbons in the ring portion, preferably 6-10 carbons in the ring portion, such as phenyl, naphthyl or tetrahydronaphthyl.

The term "heteroaryl" as employed herein refers to groups having 5 to 14 ring atoms; 6, 10 or 14 π electrons shared in a cyclic array; and containing carbon atoms and 1, 2 or 3 oxygen, nitrogen or sulfur heteroatoms (where examples of heteroaryl groups are: thienyl, benzo[b]thienyl, naphtho[2,3-b]thienyl, thianthrenyl, furyl, pyranyl, isobenzofuranyl, benzoxazolyl, chromenyl, xanthenyl, phenoxathiinyl, 2*H*-pyrrolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolizinyl, isoindolyl, 3*H*-indolyl, indolyl, indazolyl, purinyl, 4*H*-quinolizinyl, isoquinolyl, quinolinyl, tetrahydroquinolinyl, phthalazinyl, naphthyridinyl, quinazolinyl, cinnolinyl, pteridinyl, 4a*H*-carbazolyl, carbazolyl, β-carbolinyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, phenazinyl, isothiazolyl, phenothiazinyl, isoxazolyl, furazanyl and phenoxazinyl groups).

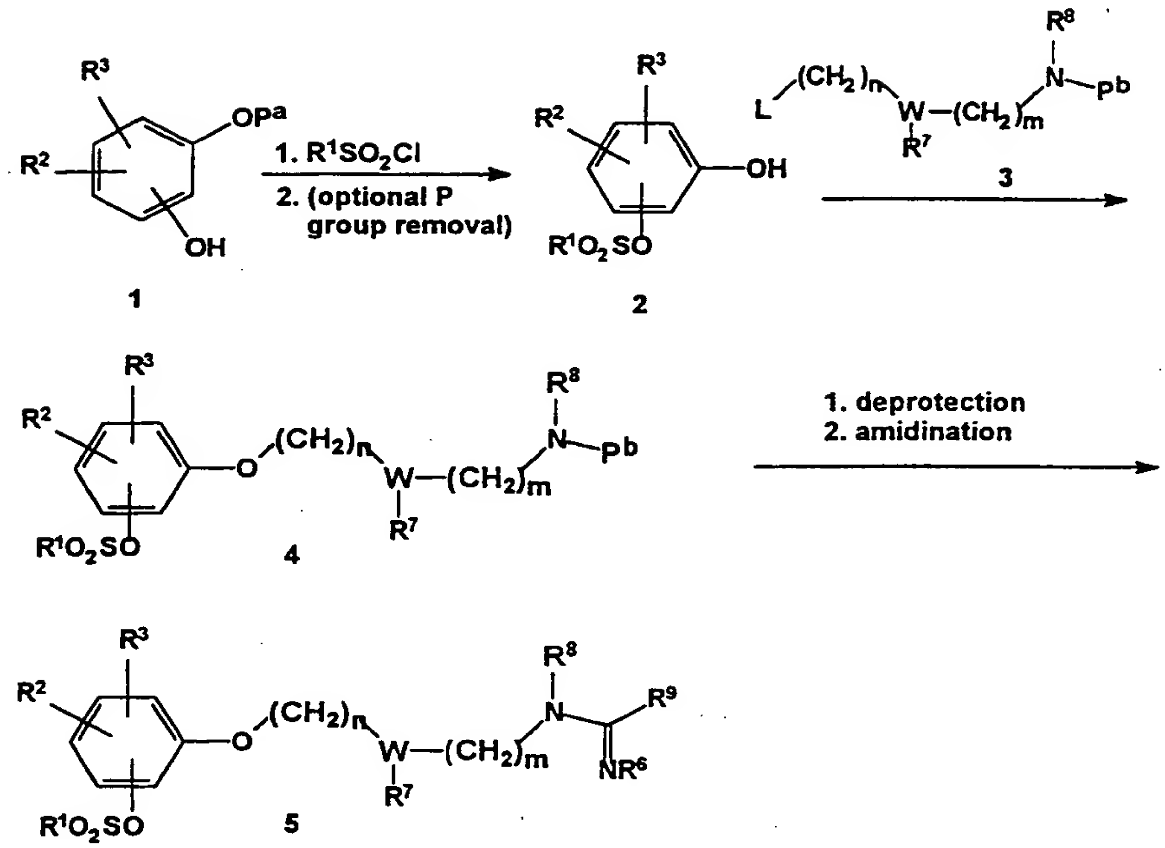
The term "aralkyl" or "arylalkyl" as employed herein by itself or as part of another group refers to C_{1-6} alkyl groups having an aryl substituent, such as benzyl, phenylethyl or 2-naphthylmethyl.

The term "cycloalkyl" as employed herein by itself or as part of another group refers to cycloalkyl groups containing 3 to 9 carbon atoms, preferably 4 to 7 carbon atoms. Typical examples are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and cyclononyl.

The term "halogen" or "halo"as employed herein by itself or as part of another group refers to chlorine, bromine, fluorine or iodine with chlorine being preferred.

Scheme **Ia** illustrates but is not limited to the preparation of compounds of Examples 1, 5, 8, 9, 11, and 12.

Scheme Ia



Each of R^1 through R^3, R^6 through R^9, n and m is as defined above; P^a is a hydroxyl protecting group or hydrogen, and P^b is an amino protecting group.

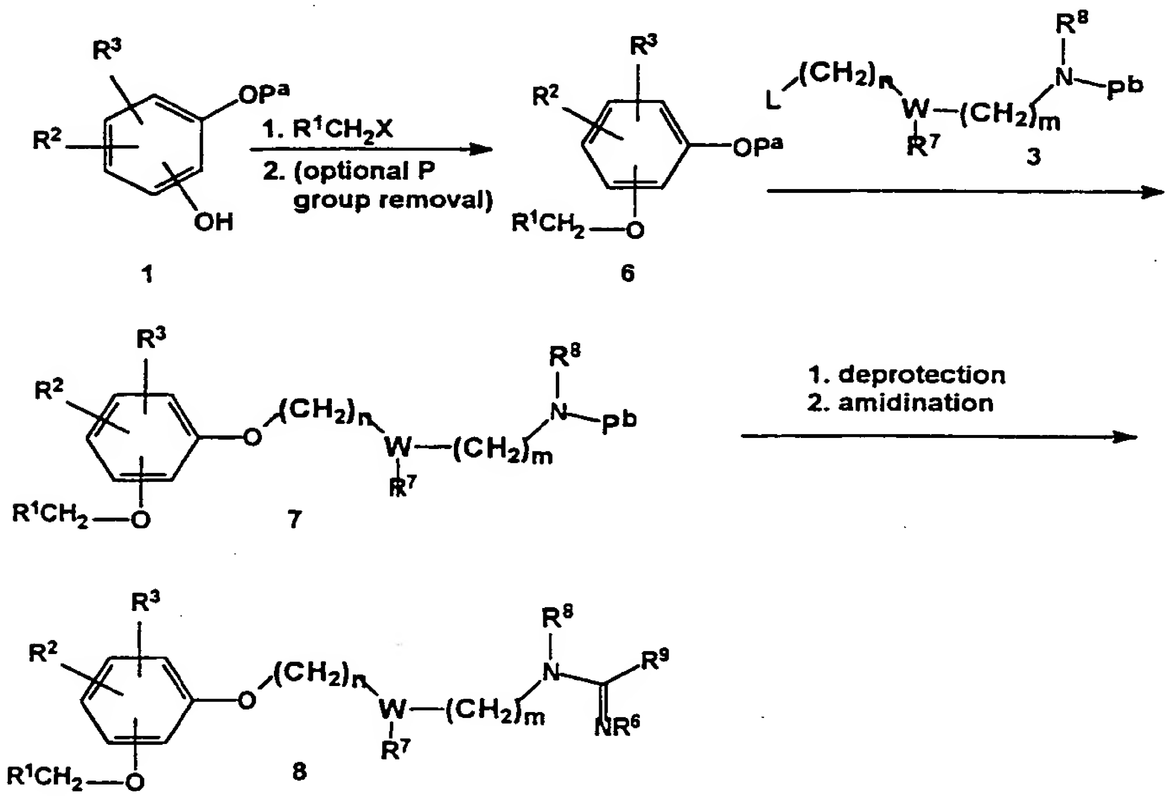
Phenols **1** (where P is H) are converted to monosulfonates **2** by treatment with appropriate sulfonyl chlorides. Preferred conditions include treating phenol **1** with a sulfonyl chloride in a biphasic system composed of ether and an aqueous phase saturated with $NaHCO_3$. Alternatively, the reaction may be effected first by deprotonating **1** with a strong base, most preferably NaH, in a polar organic solvent, such as DMF or tetrahydrofuran, followed by treating the deprotonated phenol with the sulfonyl chloride. Still alternatively, phenol **1**, in a typical organic solvent, such as methylene chloride, may be converted to **2** by treating the phenol with sulfonyl chloride in the presence of an amine base, such as N-methylmorpholine.

Phenols **1** may be monoprotected (P^a is a protecting group) with a variety of protecting groups known in the art, such as esters and benzyl ethers (Green, T.W. & Wuts, P.G.M., *Protective Groups in Organic Synthesis,* 2nd edition, John Wiley and Sons, Inc., New York (1991)). Deprotection of the hydroxyl groups is routinely accomplished using reaction conditions well-known in the art. For example, deprotection of benzyl ethers may be effected through catalytic hydrogenation using palladium on carbon as a catalyst in solvents such as ethanol or tetrahydrofuran. Deprotection of an acetate is accomplished by basic hydrolysis, most preferably with sodium hydroxide in aqueous tetrahydrofuran.

Phenols **2** are coupled to **3** (for L = OH) using a Mitsunobu coupling procedure (Mitsunobu, O., *Synthesis* 1 (1981)) to provide **4**. Preferred coupling conditions include using a trialkylphosphine or triarylphosphine, such as triphenylphosphine, in a suitable solvent such as tetrahydrofuran or methylene chloride, and a dialkyl azodicarboxylate, such as diethyl azodicarboxylate. In some cases, it is advantageous to add an amine base such as N-methylmorpholine. The amine terminus of **3** is protected with a protecting group P^b that is readily removed from **4**. Amino-protecting groups are well known in the art (Greene, T.W. & Wuts, P.G.M., *Protective Groups in Organic Synthesis*, 2nd edition, John Wiley and Sons, Inc., New York (1991)). Deprotection of the amino group is effected by employing reaction conditions that are well known in the art. For example, the *t*-butoxycarbonyl (BOC) may be removed by exposure to strongly acidic medium, such as hydrogen chloride, in a suitable solvent, such as dioxane, or a mixed trifluoroacetic acid/methylene chloride solvent system. Benzyloxycarbonyl (CBz) groups may be removed by hydrogen using palladium on carbon as a catalyst in solvents such as ethanol or tetrahydrofuran. The resulting amine is then converted to amidine **5** in a manner similar to the procedure described by Nagahara *et. al., J. Med. Chem. 37*(8):1200-1207 (1994) wherein the amine is treated with an appropriate imidate in the presence of a base such as N,N-diisopropylethylamine in an appropriate solvent such as DMF. Alternatively, the amine is treated with an appropriate imidate in the presence of a base, such as sodium hydroxide, in an appropriate solvent, such as methanol.

Scheme *Ib* illustrates but is not limited to the preparation of compounds of Examples 2 and 13.

Scheme Ib



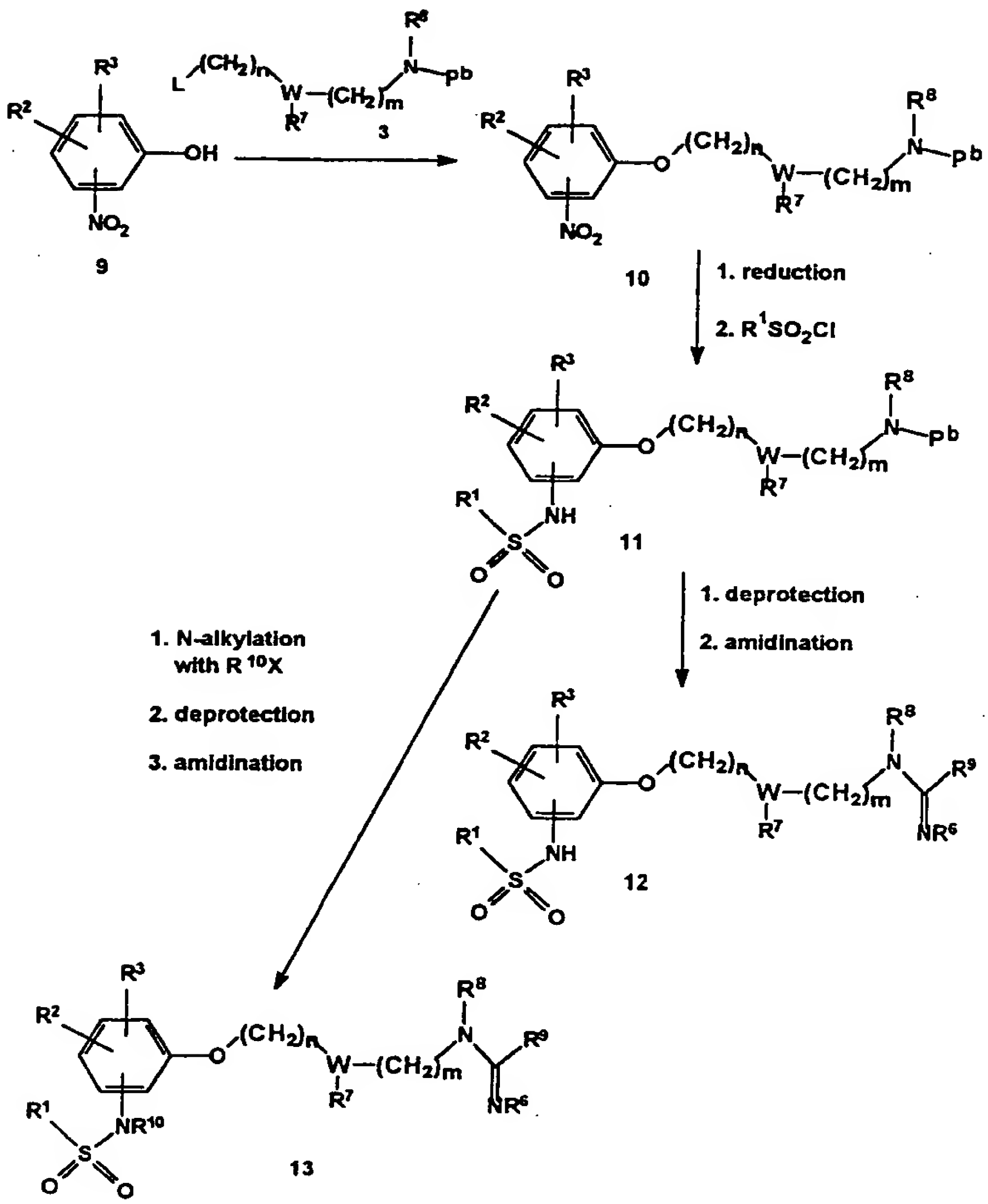
R^1-R^3, R^6-R^8, n, m P^a and P^b are each as defined above.

Aryl ethers **8** are synthesized in a fashion analogous to synthesis of **5**. Phenol **1** (P is H) is converted to derivative **6** by treating **1** with a strong base, preferably NaH, in a suitable solvent such as DMF, followed by addition of a reactive alkyl or benzyl compound, R^1CH_2X (where X is a reactive functional group such as iodide, chloride, bromide or alkylsulfonate). Alternatively, the Mitsunobu Reaction may be used with an appropriate R^1CH_2X (X = OH) using the reaction conditions described above. The use of suitable alcohol protecting groups (P^a), such as esters, to suppress over-alkylation, is well known in the art (Greene, T.W. & Wuts, P.G.M., *Protective Groups in Organic Synthysis*, 2nd edition, John Wiley and Sons, Inc., New York (1991)). The protecting group

may then be removed using well-known techniques, for example by hydrolysis with aqueous NaOH, when an ester protecting group is employed. Phenol **6** is then converted to amidine **8** using the conditions described for formation of 5.

Scheme **II** illustrates but is not limited to the preparation of compounds Examples 3, 9 and 10.

Scheme II



R^1-R^3, R^6-R^{10}, n, m, P^a and P^b are as defined above.

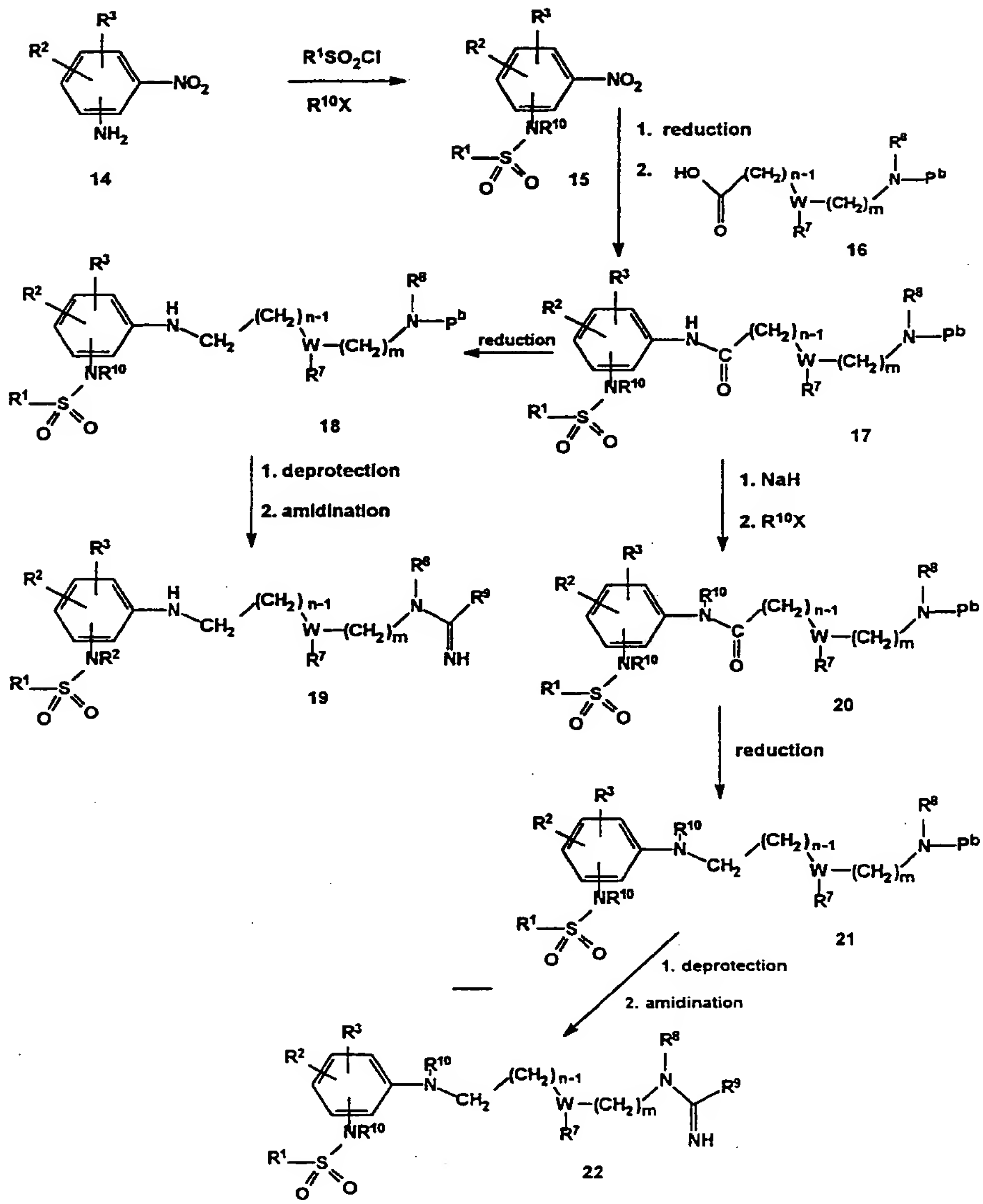
According to Scheme II, a nitrophenol **9** may be coupled to compound **3** by standard techniques. Preferably, the reaction is effected by the Mitsunobu reaction (where L is OH). Alternatively, **9** may be treated with a base, such as NaH, in a suitable solvent such as DMF or THF, followed by addition of **3** (where

L is a reactive group, such as Cl, Br, I or alkylsulfonate). The nitro group is thereafter reduced, for example, by catalytic reduction using palladium on carbon in a suitable solvent such as ethanol or tetrahydrofuran. The resulting product in then treated with an appropriate sulfonyl chloride (R^1SO_2Cl) to provide **11.** Removal of the amine protecting group P^b is accomplished by techniques known in the art. For example, the *t*-butoxycarbonyl (BOC) is removed by exposure to a strongly acidic medium, such as hydrogen chloride in a suitable solvent such as dioxane or trifluoroacetic acid in methylene chloride. Benzyloxycarbonyl (CBz) groups are removed by catalytic hydrogen using palladium on carbon as a catalyst in solvents such as ethanol or tetrahydrofuran.

The resulting amine is then converted to amidine **12** in a manner similar to the procedure described by Nagahara *et. al.*, *J. Med. Chem.* *37*(8):1200-1207 (1994) wherein the amine is treated with an appropriate imidate in the presence of a base such as N,N-diisopropylethylamine in an appropriate solvent such as DMF. Alternatively, the amine is treated with an appropriate imidate in the presence of a base such as sodium hydroxide as base in an appropriate solvent such as methanol. N-Substituted sulfonamide derivative **13** is obtained by alkylation of **11** employing a suitable alkylating agent ($R^{10}X$) in the presence of a base, most preferably Cs_2CO_3 using a polar solvent such as DMF. Deprotection and amidination are then executed in a manner similar to the conversion of **11** to **12**.

Scheme **III** illustrates but is not limited to the preparation of compounds of Example 4.

Scheme III

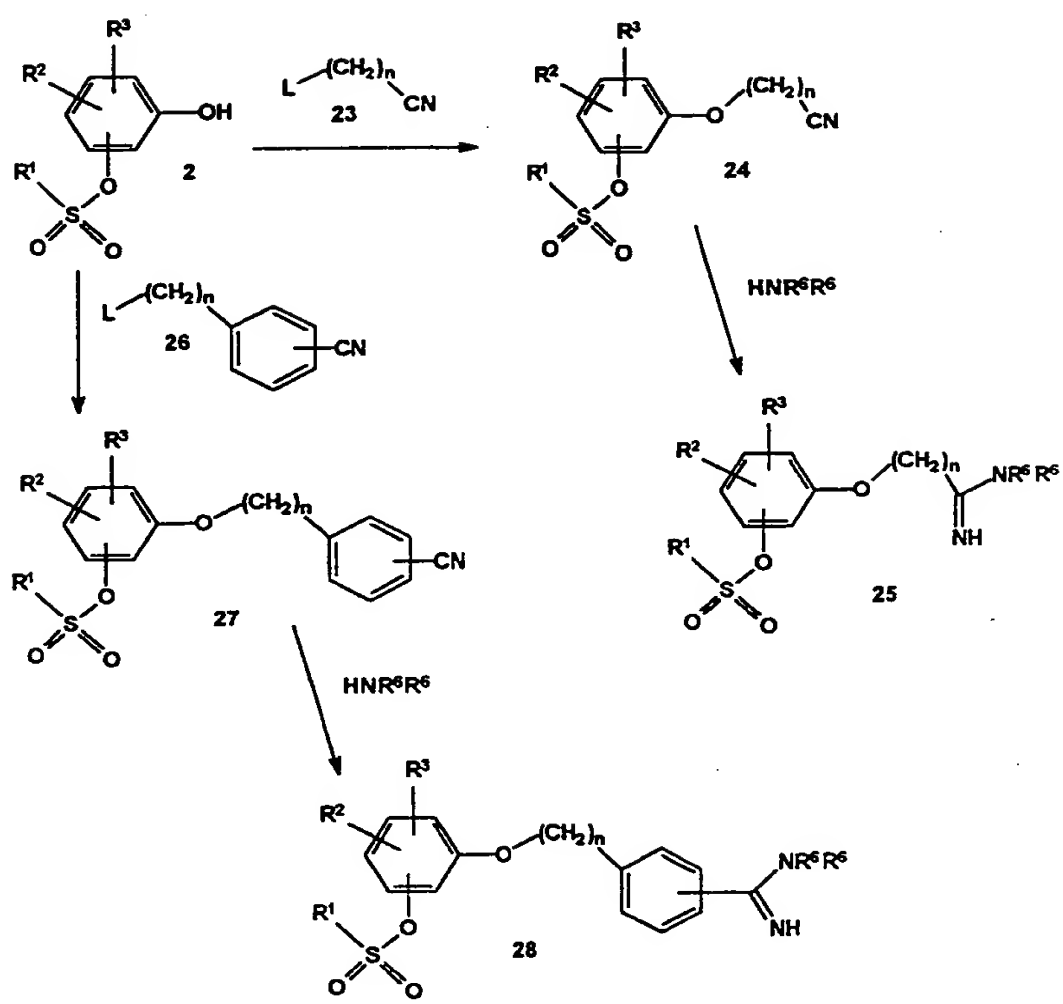

R¹SO₂Cl
R¹⁰X
1. reduction
2.
reduction
1. deprotection
2. amidination
1. NaH
2. R¹⁰X
reduction
1. deprotection
2. amidination
14
15
16
17
18
19
20
21
22

R^1-R^3, R^7-R^{10}, n, m and P^b are each as defined above.

According to Scheme **III**, nitroaniline **14** is converted to a sulfonamide by treatment with an appropriate sulfonyl chloride R^1SO_2Cl in the presence of a weak base, such as N-methylmorpholine. The resulting sulfonamide nitrogen is alkylated with a suitable alkylating agent ($R^{10}X$) in the presence of a base, preferably an alkali metal carbonate such as Cs_2CO_3 or K_2CO_3, using a polar solvent, such as DMF, to provide intermediate **15**. After reduction of the nitro group, the resulting aniline is coupled to a carboxylic acid, **16**, to provide amide **17**. Amide coupling may be performed using any of a number of common peptide coupling reagents. Preferably, one of 1,3-dicyclohexylcarbodiimide or Castro's reagent (BOP) are employed (B. Castro *et al., Tetrahedron Lett.*:1219 (1975)). Alternatively, **17** may be formed by coupling the aniline with the corresponding acid chloride of acid **16** in the presence of an acid scavenger, such as N-methylmorpholine. Amide **17** is converted to amine **18** by reduction of the amide functionality with an appropriate hydride reagent, preferably borane-THF complex or chlorotrimethylsilane and lithium borohydride. This reaction occurs in a suitable polar solvent, such as THF. Removal of the amine protecting group P^b and formation of the amidine as described in Scheme **II** provides the desired compound **19**. Alternatively the amide nitrogen may be alkylated using a strong base, such as sodium hydride, in a suitable polar solvent such as DMF, followed by treatment with an alkylating agent ($R^{10}X$) to afford intermediate **20**. Reduction of the amide, as executed in the formation of **18**, to give **21** followed by deprotection and amidination as previously described provides the analogous compound **22**.

Scheme **IV** illustrates but is not limited to the preparation of compounds of Examples 6, 7, 14, 15, 16, 17 and 18.

Scheme IV



R^1-R^3, R^6 and n are each as defined above.

Monosulfonates **2** are converted to cyano derivatives **24** by exposing **2** to a base, most preferably sodium hydride in a suitable solvent such as DMF, followed by addition **23**, where L is a reactive group such as iodide, chloride, bromide, alkyl sulfonate, or aryl sulfonate. Alternatively, the Mitsunobu Reaction may be used with an appropriate alcohol **23**, where L = OH. The nitrile is submitted to amidino formation conditions such as those described by Nagahara

et. al., *J. Med. Chem.* *37*(8):1200-1207 (1994), wherein the nitrile is first exposed to a strong acid, preferably hydrogen chloride, in a suitable alcoholic solvent, preferably methanol or ethanol, which converts the nitrile to an imidate. Following brief isolation, the imidate is treated with an appropriate amine HNR^6R^6 to effect formation of **25**. Similarly, benzamidines **28** are prepared from **2** using appropriate benzonitrile derivatives **26**.

It is to be understood that in each of the above-mentioned schemes, an additional substituent, R^4, may be present on the phenyl ring of the starting material.

For medicinal use, the pharmaceutically acceptable acid addition salts, those salts in which the anion does not contribute significantly to toxicity or pharmacological activity of the organic cation, are preferred. The acid addition salts are obtained either by reaction of an organic base of Formulae ***I-XI*** with an organic or inorganic acid, preferably by contact in solution, or by any of the standard methods detailed in the literature available to any practitioner skilled in the art. Examples of useful organic acids are carboxylic acids such as maleic acid, acetic acid, tartaric acid, propionic acid, fumaric acid, isethionic acid, succinic acid, cyclamic acid, pivalic acid and the like; useful inorganic acids are hydrohalide acids such as HCl, HBr, HI; sulfuric acid; phosphoric acid and the like. Preferred acids for forming acid addition salts include HCl and acetic acid.

The compounds of the present invention represent a novel class of potent inhibitors of metallo, acid, thiol and serine proteases. Examples of the serine proteases inhibited by compounds within the scope of the invention include leukocyte neutrophil elastase, a proteolytic enzyme implicated in the pathogenesis of emphysema; chymotrypsin and trypsin, digestive enzymes; pancreatic elastase, and cathepsin G, a chymotrypsin-like protease also associated with leukocytes; thrombin and factor Xa, proteolytic enzymes in the blood coagulation pathway. Inhibition of thermolysin, a metalloprotease, and pepsin, an acid protease, are also contemplated uses of compounds of the present invention. The compounds of the present invention are preferably employed to inhibit trypsin-like proteases.

An end use application of the compounds that inhibit chymotrypsin and trypsin is in the treatment of pancreatitis. For their end-use application, the potency and other biochemical parameters of the enzyme-inhibiting characteristics of the compounds of the present invention is readily ascertained by standard biochemical techniques well-known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated, as determined by the attending diagnostician. It is expected that a useful dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect.

Compounds of the present invention that are distinguished by their ability to inhibit either factor Xa or thrombin may be employed for a number of therapeutic purposes. As factor Xa or thrombin inhibitors, compounds of the present invention inhibit thrombin production. Therefore, these compounds are useful for the treatment or prophylaxis of states characterized by abnormal venous or arterial thrombosis involving either thrombin production or action. These states include, but are not limited to, deep vein thrombosis; disseminated intravascular coagulopathy which occurs during septic shock, viral infections and cancer; myocardial infarction; stroke; coronary artery bypass; hip replacement; and thrombus formation resulting from either thrombolytic therapy or percutaneous transluminal coronary angioplasty (PCTA). The compounds of the present invention may also be used as an anticoagulant in extracorporeal blood circuits.

By virtue of the effects of both factor Xa and thrombin on a host of cell types, such as smooth muscle cells, endothelial cells and neutrophils, the compounds of the present invention find additional use in the treatment or prophylaxis of adult respiratory distress syndrome; inflammatory responses, such as edema; reperfusion damage; atherosclerosis; and restenosis following an injury such as balloon angioplasty, atherectomy, and arterial stent placement.

The compounds of the present invention may be useful in treating neoplasia and metastasis as well as neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease.

When employed as thrombin or factor Xa inhibitors, the compounds of the present invention may be administered in an effective amount within the dosage range of about 0.1 to about 500 mg/kg, preferably between 0.1 to 10 mg/kg body weight, on a regimen in single or 2-4 divided daily doses.

When employed as inhibitors of thrombin, the compounds of the present invention may be used in combination with thrombolytic agents such as tissue plasminogen activator, streptokinase, and urokinase. Additionally, the compounds of the present invention may be used in combination with other antithrombotic or anticoagulant drugs such as, but not limited to, fibrinogen antagonists and thromboxane receptor antagonists.

Human leucocyte elastase is released by polymorphonuclear leukocytes at sites of inflammation and thus is a contributing cause for a number of disease states. Thus, compounds of the present invention are expected to have an anti-inflammatory effect useful in the treatment of gout, rheumatoid arthritis and other inflammatory diseases, and in the treatment of emphysema. Cathepsin G has also been implicated in the disease states of arthritis, gout and emphysema, and in addition, glomerulonephritis and lung infestations caused by infections in the lung. In their end-use application the enzyme inhibitory properties of the compounds of Formulae ***I-XI*** is readily ascertained by standard biochemical techniques that are well-known in the art.

The neutrophil elastase inhibitory properites of compounds within the scope of the present invention are determined by the following method. Neutrophil elastase is prepared by the procedure described by Baugh *et al.*, *Biochemistry 15*: 836 (1979). Enzyme assays are conducted substantially according to the procedure disclosed by Nakajima *et al.*, *J. Biol. Chem. 254*: 4027 (1979), in assay mixtures containing 0.10 M Hepes (N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid) buffer, pH 7.5; 0.5 M NaCl; 10% dimethylsulfoxide; and 1.50 x 10^{-4} M MeOSuc-Ala-Ala-Pro-Val-*p*-nitroanilide as substrate. Inhibitors are evaluated by comparing enzymatic activity measured in the presence and absence of inhibitor.

The Cathepsin G inhibitory properties of compounds within the scope of the present invention are determined by the following method. A preparation of partially purified human Cathepsin G is obtained by the procedure of Baugh *et al.*, *Biochemistry 15*: 836 (1979). Leukocyte granules are a major source for the preparation of leukocyte elastase and cathepsin G (chymotrypsin-like activity). Leukocytes are lysed and granules are isolated. The leukocyte granules are extracted with 0.20 M sodium acetate, pH 4.0, and extracts are dialyzed against 0.05 M Tris buffer, pH 8.0 containing 0.05 M NaCl overnight at 4°C. A protein fraction precipitates during dialysis and is isolated by centrifugation. This fraction contains most of the chymotrypsin-like activity of leukocyte granules. Specific substrates are prepared for each enzyme, namely MeOSuc-Ala-Ala-Pro-Val-*p*-nitroanilide and Suc-Ala-Ala-Pro-Phe-*p*-nitroanilide. The latter is not hydrolyzed by leukocyte elastase. Enzyme preparations are assayed in 2.00 mL of 0.10 M Hepes buffer, pH 7.5, containing 0.50 M NaCl, 10% dimethylsulfoxide and 0.0020 M Suc-Ala-Ala-Pro-Phe-*p*-nitroanilide as a substrate. Hydrolysis of the p-nitroanilide substrate is monitored at 405 nm and at 25°C.

Useful dose range for the application of compounds of the present invention as neutrophil elastase inhibitors and as Cathepsin G inhibitors will of course depend upon the nature and severity of the disease state, as determined by the attending diagnostician, with the range of 0.01 to 10 mg/kg of body weight, per day, being useful for the aforementioned disease states.

Compounds of the present invention that inhibit urokinase or plasminogen activator are potentially useful in treating excessive cell growth disease state. As such the compounds of the present invention may also be useful in the treatment of benign prostatic hypertrophy and prostatic carcinoma, the treatment of psoriasis, and in their use as abortifacients. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of the present invention are readily ascertained by standard biochemical techniques well-known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity

of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect.

Additional uses for compounds of the present invention include analysis of commercial reagent enzymes for active site concentration. For example, chymotrypsin is supplied as a standard reagent for use in clinical quantitation of chymotrypsin activity in pancreatic juices and feces. Such assays are diagnostic for gastrointestinal and pancreatic disorders. Pancreatic elastase is also supplied commercially as a reagent for quantitation of α_1-antitrypsin in plasma. Plasma α_1-antitrypsin increases in concentration during the course of several inflammatory diseases, and α_1-antitrypsin deficiencies are associated with increased incidence of lung disease. Compounds of the present invention can be used to enhance the accuracy and reproducibility of this assay by titrametric standardization of the commercial elastase supplied as a reagent. See, U.S. Patent No. 4,499,082.

Protease activity in certain protein extracts during purification of particular proteins is a recurring problem which can complicate and compromise the results of protein isolation procedures. Certain proteases present in such extracts can be inhibited during purification steps by compounds of the present invention, which bind tightly to various proteolytic enzymes.

The pharmaceutical compositions of the invention can be administered to any animal that can experience the beneficial effects of the compounds of the invention. Foremost among such animals are humans, although the invention is not intended to be so limited.

The pharmaceutical compositions of the present invention can be administered by any means that achieve their intended purpose. For example, administration can be by parenteral, subcutaneous, intravenous, intramuscular, intraperitoneal, transdermal, buccal, or ocular routes. Alternatively, or concurrently, administration can be by the oral route. The dosage administered will be dependent upon the age, health, and weight of the recipient, kind of

concurrent treatment, if any, frequency of treatment, and the nature of the effect desired.

In addition to the pharmacologically active compounds, the new pharmaceutical preparations can contain suitable pharmaceutically acceptable carriers comprising excipients and auxiliaries that facilitate processing of the active compounds into preparations that can be used pharmaceutically.

The pharmaceutical preparations of the present invention are manufactured in a manner that is, itself, known, for example, by means of conventional mixing, granulating, dragee-making, dissolving, or lyophilizing processes. Thus, pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid excipients, optionally grinding the resulting mixture and processing the mixture of granules, after adding suitable auxiliaries, if desired or necessary, to obtain tablets or dragee cores.

Suitable excipients are, in particular, fillers such as saccharides, for example, lactose or sucrose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example, tricalcium phosphate or calcium hydrogen phosphate, as well as binders, such as, starch paste, using, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, tragacanth, methyl cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, and/or polyvinyl pyrrolidone. If desired, disintegrating agents can be added, such as, the above-mentioned starches and also carboxymethyl-starch, cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof, such as, sodium alginate. Auxiliaries are, above all, flow-regulating agents and lubricants, for example, silica, talc, stearic acid or salts thereof, such as, magnesium stearate or calcium stearate, and/or polyethylene glycol. Dragee cores are provided with suitable coatings that, if desired, are resistant to gastric juices. For this purpose, concentrated saccharide solutions can be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, polyethylene glycol, and/or titanium dioxide, lacquer solutions and suitable organic solvents or solvent mixtures. In order to produce coatings resistant to gastric juices, solutions of suitable cellulose

preparations, such as, acetylcellulose phthalate or hydroxypropylmethyl-cellulose phthalate, are used. Dye stuffs or pigments can be added to the tablets or dragee coatings, for example, for identification or in order to characterize combinations of active compound doses.

Other pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as, glycerol or sorbitol. The push-fit capsules can contain the active compounds in the form of granules that may be mixed with fillers such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds are preferably dissolved or suspended in suitable liquids, such as, fatty oils or liquid paraffin. In addition, stabilizers may be added.

Suitable formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form, for example, water-soluble salts, alkaline solutions and cyclodextrin inclusion complexes. Especially preferred alkaline salts are ammonium salts prepared, for example, with Tris, choline hydroxide, Bis-Tris propane, N-methylglucamine, or arginine. One or more modified or unmodified cyclodextrins can be employed to stabilize and increase the water solubility of compounds of the present invention. Useful cyclodextrins for this purpose are disclosed in U.S. Patent Nos. 4,727,064, 4,764,604, and 5,024,998.

In addition, suspensions of the active compounds as appropriate oily injection suspensions can be administered. Suitable lipophilic solvents or vehicles include fatty oils, for example, sesame oil, or synthetic fatty acid esters, for example, ethyl oleate or triglycerides or polyethylene glycol-400 (the compounds are soluble in PEG-400). Aqueous injection suspensions can contain substances that increase the viscosity of the suspension, for example, sodium carboxymethyl cellulose, sorbitol, and/or dextran. Optionally, the suspension may also contain stabilizers.

The following examples are illustrative, but not limiting, of the method and compositions of the present invention. Other suitable modifications and adaptations of the variety of conditions and parameters normally encountered and obvious to those skilled in the art are within the spirit and scope of the invention.

Examples

Example 1

2-Chlorobenzenesulfonic acid 3-[(1-acetimidoylpiperidin-4-yl)methoxy]-5-methylphenyl ester hydrochloride

a) ***N-*tert*-butoxycarbonylisonipecotic acid***

Di-*tert*-butyl dicarbonate (6.55 g, 30 mmol) was added to the mixture of isonipecotic acid (3.90 g, 30 mmol) and $NaHCO_3$ (5.05 g, 60 mmol) in 1:1 1,4-dioxane/water (100 mL), and the mixture was stirred at room temperature overnight. The reaction mixture was evaporated *in vacuo*, acidified to pH 6 using 10% citric acid and extracted with ethyl acetate (3x100 mL). The organic phase was washed with brine (2x50 mL) and dried over Na_2SO_4. The solvent was evaporated to give the title compound as a white solid (6.25 g, 91%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 9 H), 1.63 (m, 2 H), 1.88 (dd, 2 H, J = 1.5, 6.6 Hz), 2.45 (m, 1 H), 2.83 (t, 2 H, J = 11.4 Hz), and 4.00 (d,.2 H, J = 6.7 Hz).

b) ***N-*tert*-Butoxycarbonyl-4-piperidinemethanol***

Borane-tetrahydrofuran (1 M, 25 mL, 25 mmol) was added slowly to N-*tert*- butoxycarbonylisonipecotic acid (5.73 g, 25 mmol), as prepared in the preceding step, in tetrahydrofuran (50 mL) at 0°C (ice-bath) over 30 min. The mixture was stirred at 0°C overnight and then warmed up to room temperature for 6 h. Water (10 mL) was added slowly and then K_2CO_3 (5 g in 50 mL water) was added. The mixture was extracted with ethyl acetate (3 x 50 mL). The organic phase was washed sequentially with saturated $NaHCO_3$ (2 x 50 mL) and

brine (2 x 50 mL), and dried over Na_2SO_4. The solvent was removed *in vacuo*, and the residue was purified by flash column chromatography (1:1 hexane/ethyl acetate) to give the title compound as white crystals (4.55 g, 84%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.13 (m, 2 H), 1.42 (s, 9 H), 1.67 (m, 4 H), 2.67 (t, 2 H, J = 12.5 Hz), 3.46 (d, 2 H, J = 3.0 Hz), and 4.09 (d, 2 H, J = 3.6 Hz).

c) 2-Chlorobenzenesulfonic acid 3-hydroxy-5-methylphenyl ester

Orcinol monohydrate (1.42 g, 10 mmol) and 2-chlorobenzenesulfonyl chloride (2.43 g, 11 mmol) were mixed in saturated $NaHCO_3$ (30 mL) and diethyl ether (30 mL). The biphasic mixture was stirred vigorously at room temperature for 2 days. The reaction mixture was quenched with 50 mL of water and extracted into ethyl acetate (3 x 50 mL). The organic phase was washed with brine (2 x 50 mL) and dried over Na_2SO_4. After removing the solvent *in vacuo*, the residue was purified by flash column chromatography (2% ethyl acetate in methylene chloride) to give the title compound as a pale-yellow liquid (2.15 g, 71%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.22 (s, 3 H), 5.24 (s, 1 H), 6.43 (s, 1 H), 6.52 (s, 2H), 7.38 (m, 1 H), 7.60 (m, 2 H), and 7.96 (dd, 1 H, J = 0.6, 3.9 Hz).

*d) 2-Chlorobenzenesulfonic acid 3-[[N-(*tert*-butoxycarbonyl)piperidin-4-yl]methoxy]-5-methylphenyl ester*

Diethyl azodicarboxylate (349 mg, 2.0 mmol) was added to a solution of 2-chlorobenzenesulfonic acid 3-hydroxy-5-methylphenyl ester (600 mg, 2.0 mmol), as prepared in the preceding step, N-*tert*-butoxylcarbonyl-4-piperidinemethanol (430 mg, 2.0 mmol), as prepared in step (b), and triphenylphosphine (525 mg, 2.0 mmol) in tetrahydrofuran (15 mL) at 0°C. The reaction mixture was stirred at 0°C for 2 h and at room temperature for 3 h. The reaction mixture was quenched with water (50 mL) and was extracted with ethyl acetate (3 x 50 mL). The organic phase was washed with saturated $NaHCO_3$ (2 x 50 mL), brine (2 x 50 mL) and dried over Na_2SO_4. The solvent removed *in vacuo* and the residue was purified by flash column chromatography (2:1 ethyl acetate/hexane) to give the title compound as a colorless syrup (895 mg, 90%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.24 (m, 2 H), 1.47 (s, 9 H), 1.76 (d, 2 H, J = 6.6 Hz), 1.89 (m, 1 H), 2.24 (s, 3 H), 2.72 (t, 2 H, J = 2.4 Hz), 3.68 (d, 2 H, J = 3.2 Hz), 4.13 (m, 2 H), 6.47 (t, 1 H, J = 2.2 Hz), 6.52 (d, 1 H, J = 0.7 Hz), 6.58 (d, 1 H, J = 0.8 Hz), 7.38 (dd, 1 H, J = 0.6, 0.8 Hz), 7.61 (m, 2 H), and 7.97 (dd, 1 H, J = 0.8, 4.0 Hz).

e) ***2-Chlorobenzenesulfonic acid 3-[(piperidin-4-yl)methoxy]-5-methylphenyl ester***

2-Chlorobenzenesulfonic acid 3-[[N-(*tert*-butoxycarbonyl)piperidin-4-yl]methoxy]-5-methylphenyl ester (745 mg, 1.5 mmol), as prepared in the preceding step, was treated with 4 N HCl in 1,4-dioxane (20 mL) at room temperature for 2 h. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (10% methanol in methylene chloride saturated with NH_3) to give the title compound as a colorless syrup (570 mg, 95%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.45 (m, 1 H), 1.94 (m, 3 H), 2.23 (s, 3 H), 2.45 (m, 1 H), 2.71 (dt, 2 H, J = 1.2, 12.3 Hz), 3.51 (m, 2 H), 3.76 (m, 2 H), 6.46 (t, 1 H, J = 2.1 Hz), 6.53 (s, 1 H), 6.58 (s, 1 H), 7.40 (t, 1 H, J = 6.5 Hz), 7.62 (m, 2 H), and 7.97 (dd,1 H, J = 1.4, 7.9 Hz). Mass spectrum (MALDI-TOF, sinapinic acid matrix) calcd. for $C_{19}H_{22}NO_4SCl$: 396.1 (M+ H), Found: 396.4.

f) ***2-Chlorobenzenesulfonic acid 3-[(1-acetimidoylpiperidin-4-yl)methoxy]-5-methylphenyl ester hydrochloride***

Triethylamine (0.5 mL) and ethyl acetimidate hydrochloride (247 mg, 2.0 mmol) were added to a solution of 2-chlorobenzenesulfonic acid 3-[(piperidin-4-yl)methoxy]-5-methylphenyl ester (396 mg, 1.0 mmol), as prepared in the preceding step, in N,N-dimethylformamide (10 mL). The reaction mixture was stirred at room temperature overnight. The N,N-dimethylformamide was removed *in vacuo* and the residue partitioned between methylene chloride (200 mL) and 10% K_2CO_3 (50 mL). The organic phase was washed with 10% K_2CO_3 (2 x 50 mL) and dried over K_2CO_3. The solvent was removed *in vacuo*, HCl-methanol (30 mL) was added, and the solution was concentrated *in vacuo*. The residue was

crystallized from methanol-ethyl acetate to give the title compound as white crystals (405 mg, 86%). ^{1}H-NMR (300 MHz, DMSO-d_6) δ 1.30 (m, 2 H), 1.82 (d, 2 H, J = 7.0 Hz), 2.05 (m, 1 H), 2.20 (s, 3 H), 2.29 (s, 3 H), 3.16 (m, 2 H), 3.77 (d, 2 H, J = 3.0 Hz), 3.92 (d, 1 H, J = 6.5 Hz), 4.17 (d, 1 H, J = 6.5 Hz), 6.46 (d, 1 H, J = 2.5 Hz), 6.49 (s, 1 H), 7.59 (t, 1 H. J = 8.0 Hz), 7.87 (m, 2 H), 7.95 (d, 1 H, J = 8.0 Hz), 8.77 (br s, 1 H), and 9.35 (br s, 1 H). Mass spectrum (MALDI-TOF, sinapinic acid matrix) calcd. for $C_{21}H_{25}N_2O_4SCl$: 437.1 (M+ H). Found: 436.8.

Example 2

3-(2-Chlorobenzyloxy)-5-methyl-1-[2-(1-acetimidoyl)piperazin-4-yl]]ethoxybenzene diacetic acid salt

a) *N-(*tert*-Butoxycarbonyl)-1-(2-hydroxyethyl)piperazine*

To a solution of 1-(2-hydroxyethyl)piperazine (5.20 g, 40 mmol) and triethylamine (6 mL 43 mmol), in 1,4-dioxane (100 mL) was added slowly di-*tert*-butyl dicarbonate (8.72 g, 40 mmol). The reaction mixture was stirred at room temperature for 2 h . The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (ethyl acetate to 2% methanol in ethyl acetate) to give the title compound as colorless oil (8.32 g, 90%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.46 (s, 9 H), 2.46 (t, 4 H), 2.55 (t, 2 H), 2.75 (br s,1 H), 3.44 (t, 4 H), and 3.63 (t, 2 H).

b) *3-(2-Chlorobenzyloxy)-5-methylphenol*

To 1.31 g (9.22 mmol) of orcinol monohydrate in 20 mL anhydrous N,N-dimethylformamide under a nitrogen atmosphere was added 220 mg (9.17 mmol) of NaH (100%). After 5 min, 1.30 mL (10.0 mmol) of 2-chlorobenzyl bromide was added. The reaction mixture was stirred for 2 h and then quenched with 1 N HCl. The reaction mixture was extracted into ethyl acetate (200 mL). The organic phase was washed with water (4 x 100 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification by flash chormatography (diethyl ether/hexane (50:50 to

100:0) gave 656 mg of the title compound as a glass. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.54 (dd, 1 H, J = 3, 7 Hz), 7.39 (dd, 1 H, J = 3, 7 Hz), 7.2 - 7.3 (m, 2 H), 6.41 (s, 1 H), 6.29 - 6.30 (m, 2 H), 5.29 (s, 2 H), and 2.28 (s, 3 H).

*c) 3-(2-Chlorobenzyloxy)-5-methyl-1-[2-[N-(*tert*-butoxycarbonyl) piperazin-4-yl]]ethoxybenzene*

To a solution of 210 mg (0.845 mmol) of 3-(2-chlorobenzyloxy)-5-methylphenol as prepared in the preceding step, 204 mg (0.887 mmol) of N-(*tert*-butoxycarbonyl)-1-(2-hydroxyethyl)piperazine, as prepared in step (a) of this Example, 287 mg (1.10 mmol) of triphenylphosphine, and 280 μL (2.5 mmol) of N-methylmorpholine in 3 mL of tetrahydrofuran was added 160 μL (1.09 mmol) of N,N-diethyl azodicarboxylate. After stirring overnight at ambient temperature, the reaction mixture was quenched with water, extracted into ethyl acetate, dried ($MgSO_4$), and purified by flash chromatography (methylene chloride/diethyl ether (8:1 to 4:1)) to give the 270 mg (59% yield) of the title compound as a gum. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.55 (dd, 1 H), 7.37 - 7.41 (m, 1 H), 7.22 - 7.3 (m, 2 H), 6.43 (s, 1 H), 6.37 (d, 2 H), 5.12 (d, 2 H), 4.08 (t, 2 H, J = 6.7 Hz), 3.45 (t, 4 H), 2.80 (t, 2 H, J = 6 Hz), 2.51 (t, 4 H), and 1.46 (s, 9 H). Mass spectrum (MALDI-TOF; gentisic acid matrix) calcd. for $C_{25}H_{33}ClN_2O_4$: 461.2 (M + H). Found: 460.9.

d) 3-(2-Chlorobenzyloxy)-5-methyl-1-[2-[piperazin-4-yl]]ethoxybenzene dihydrochloride

A solution of 251 mg (0.544 mmol) of 3-(2-chlorobenzyloxy)-5-methyl-1-[2-[N-(*tert*-butoxycarbonyl)piperazin-4-yl]]ethoxybenzene as prepared in the preceding step, in 3 mL of methylene chloride and 500 δ of 4 N HCl in dioxane was stirred for 1 h. Another 1 mL of 4 N HCl in dioxane was added. After stirring for another 15 min, the reaction mixture was triturated with diethyl ether. The product was collected by filtration to provide 127 mg of the title compound as a colorless solid. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.50 (br s, 2 H), 7.58 - 6.61 (m, 1 H), 7.51 - 7.57 (m, 1 H), 7.37 - 7.40 (m, 2 H), 6.53 (s, 1 H), 6.49 (s,

3 H), 5.12 (s, 2 H), 4.35 (br s, 2 H), and 2.27 (s, 3 H). Mass spectrum (MALDI-TOF; α-cyano-4-hydroxycinnamic acid matrix) calcd. for $C_{20}H_{25}ClN_2O_2$: 361.2 (M + H). Found: 360.9.

e) 3-(2-Chlorobenzyloxy)-5-methyl-1-[2-[1-(acetymidoyl)piperazin-4-yl]]ethoxybenzene diacetic acid salt

A solution of 104 mg (0.240 mmol) of 3-(2-chlorobenzyloxy)-5-methyl-1-2-[N-(*tert*-butoxycarbonyl)piperazin-4-yl]]ethoxybenzene, as prepared in the preceding step, 90 mg (0.732 mmol) of ethyl acetimidate hydrochloride in 1 mL of N,N-dimethylformamide containing 260 μL of N,N-diisopropylethylamine was stirred at ambient temperature for 2 days. The solvent was removed *in vacuo*. The residue was quenched with 1 N sodium hydroxide, extracted into methylene chloride, dried (K_2CO_3), and concentrated. The residue was dissolved in 1 mL methylene chloride and then treated with 500 μL glacial acetic acid. The solution was then purified by preparative thin layer chromatography using methylene chloride/glacial acetic acid/methanol (53:13:34) as developing solvent to give 32.6 mg of the title compound as a colorless foam after repeated concentrations from diethyl ether/methylene chloride/hexane. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9 - 9.0 (br s, 2 H), 7.50 - 7.60 (m, 2 H), 7.38 - 7.41 (m, 2 H), 6.48 (s, 1 H), 6.39 (s, 2 H), 5.11 (s, 2 H), 4.06 (t, 2 H), 3.53 - 3.56 (m, 4 H), 2.74 (t, 2 H), 2.60 (t, 4 H), 2.27 (s, 3 H), 2.24 (s, 3 H), and 1.85 (br s, 6 H). Mass spectrum (MALDI-TOF; α-cyano-4-hydroxycinnamic acid matrix) calcd. for $C_{22}H_{28}ClN_3O_2$: 402.2 (M + H). Found: 401.8.

Example 3

N-[2-(N,N-dimethylamino)ethyl]-N-[2-[[4-(1-acetimidoyl)amino]butoxy]-4-methylphenyl]benzenesulfonamide dihydrochloride.

*a) 2-[(4-(*tert*-Butoxycarbonylamino)butoxy]-4-methylnitrobenzene.*

To 252 mg (1.33 mmol) 4-(*tert*-butoxycarbonylamino)butanol, 407 mg (2.66 mmol) 4-methyl-2-nitrophenol and 383 mg (1.46 mmol) triphenylphosphine

in 1.0 mL of anhydrous tetrahydrofuran under nitrogen was added 336 μL (1.46 mmol) of diethyl azodicarboxylate. After stirring for 1 h, the mixture was concentrated to a yellow syrup. Chromatography on a Waters Associates 10 g silica Sep-Pak SPE column eluting with 10-12% ethyl acetate - hexane afforded 422 mg (98%) of the title compound as a colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.64 (d, 1 H, J = 2.0 Hz), 7.30 (dd, 1 H, J = 8.5, 2.2 Hz), 6.95 (d, 1 H, J = 8.5 Hz), 4.64 (br s, 1 H), 4.09 (t, 2 H, J = 6.1 Hz), 3.19 (q, 2 H, J = 6.5 Hz), 2.34 (s, 3 H), 1.86 (m, 2 H), 1.69 (m, 2 H), and 1.44 (s, 9 H). Mass spectrum (MALDI-TOF, gentisic acid matrix) calcd. for $C_{16}H_{24}N_2O_5$: 347.2 (M + H). Found: 347.3.

b) *2-[(4-(*tert-*Butoxycarbonylamino)butoxy]-4-methylaniline.*

To a solution of 390 mg (1.20 mmol) of 2-[(4-(*tert*-butoxycarbonylamino) butoxy]-4-methylnitrobenzene, as prepared in preceding step, in 1.5 mL of tetrahydrofuran was added 39 mg of 10% palladium on carbon and the mixture stirred under a balloon of hydrogen for 20 h. The mixture was filtered (Celite) washing with 3 mL of tetrahydrofuran and concentrated to 339 mg (96%) of the title compound as a colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.66 (d, 1 H, J = 8.0 Hz), 6.55 (dd, 1 H, J = 2.0 Hz), 6.49 (d, 1 H, J = 8.0 Hz), 4.59 (br s, 1 H), 3.98 (t, 2 H, J = 6.3 Hz), 3.19 (q, 2 H, J = 6.6 Hz), 2.21 (s, 3 H), 1.82 (m, 2 H), 1.67 (m, 2 H), 1.57 (br s, 2 H), and 1.44 (s, 9 H). Mass spectrum (MALDI-TOF, gentisic acid matrix) calcd. for $C_{16}H_{26}N_2O_3$: 317.2 (M + Na). Found: 317.2.

c) *N-[2-[4-(*tert-*Butoxycarbonylamino)-butoxy]-4-methylphenyl] benzenesulfonamide*

To 216 mg (0.734 mmol) of 2-[(4-(*tert*-butoxycarbonylamino)butoxy]-4-methylaniline, as prepared in preceding step, and 101 μL (0.918 mmol) of 4-methylmorpholine in 3.0 mL of dichloromethane was added 143 μL (0.807 mmol) of benzenesulfonyl chloride. The solution was stirred for 45 min, diluted with 30 mL of dichloromethane and washed with 10% citric acid (2 x 30 mL), saturated $NaHCO_3$ (2 x 30 mL), and brine (30 mL). The solution was dried

(Na_2SO_4) and concentrated to 342 mg of a faintly amber solid. Chromatography on a Waters Associates 10 g silica Sep-Pak SPE column eluting with a gradient of 0 - 4% ethyl acetate - dichloromethane afforded 282 mg (88%) of the title compound as a white crystalline solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.72 (m, 2 H), 7.50 (m, 1 H), 7.40 (m, 3 H), 6.94 (s, 1 H), 6.83 (dd, 1 H, J = 8.3, 2.1 Hz), 6.59 (d, 1 H, J = 8.3 Hz), 4.54 (br s, 1 H), 3.70 (t, 2 H, J = 6.3 Hz), 3.19 (q, 2 H, J = 6.5 Hz), 2.27 (s, 3 H), 1.62 (m, 2 H), 1.48 (m, 2 H), and 1.46 (s, 9 H). Mass spectrum (MALDI-TOF, gentisic acid matrix) calcd. for $C_{22}H_{30}N_2O_5S$: 457.2 (M + Na). Found: 457.7.

*d) N-[2-(N,N-Dimethylamino)ethyl]-N-[2-[4-(*tert*-butoxycarbonylamino)-butoxy]-4-methylphenyl]benzenesulfonamide*

To a solution of 82.2 mg (0.189 mmol) of N-[2-[4-(*tert*-butoxycarbonylamino)butoxy]-4-methylphenyl]benzenesulfonamide, as prepared in preceding step, in 1.5 mL of anhydrous N,N-dimethylformamide was added 78.3 mg (0.567 mmol) of powdered anhydrous potassium carbonate and 30 mg (0.208 mmol) of N,N-dimethylaminoethyl chloride hydrochloride. After stirring at 50°C for 21 h, the mixture was partitioned between 10 mL of ethyl acetate and 10 mL of water. The organic layer was washed with water (10 mL) and brine (10 mL), dried (Na_2SO_4) and concentrated to give 93.7 mg of a colorless oil. Chromatography on a 10 g Waters Associates Sep-Pak silica SPE column with 50% ethyl acetate - dichloromethane afforded a small amount of unreacted starting material (7.4 mg) followed by 10% methanol - dichloromethane afforded 67.2 mg (77% based on recovered starting material) of the title compound as a colorless resin. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.67 (m, 2 H), 7.53 (m, 1 H), 7.43 (m, 2 H), 7.11 (d, 1 H, J = 2.0 Hz), 7.06 (dd, 1 H, J = 8.4, 1.7 Hz), 6.66 (d, 1 H, J = 8.4), 4.53 (br s, 1 H), 3.4-3.8 (br m, 4 H), 3.04 (q, 2 H, J = 6.3 Hz), 2.88 (m, 2 H), 2.28 (s, 3 H), 2.22 (s, 6 H), 1.46 (s, 9 H), and 1.33 (m, 4 H). Mass spectrum (MALDI-TOF, α-cyano-4-hydroxycinnamic acid matrix) calcd. for $C_{26}H_{39}N_3O_5S$: 506.3 (M + H), 528.3 (M + Na). Found: 506.5, 528.8.

e) *N-[2-(N,N-Dimethylamino)ethyl]-N-[2-[[4-(1-acetimidoyl) amino]butoxy]-4-methylphenyl]benzenesulfonamide dihydrochloride*

To a solution of 82.0 mg (0.162 mmol) of N-[2-(N,N-dimethylamino) ethyl]-N-[2-[4-(*tert*-butoxycarbonylamino)butoxy]-4-methylphenyl] benzenesulfonamide, as prepared in preceding step, in 2.0 mL of anhydrous dichloromethane was added 2.0 mL of trifluoroacetic acid. After stirring for 15 min, the solution was concentrated and placed under vacuum (0.5 torr/1 h) to afford a colorless oil. This residue in 0.75 mL of anhydrous N,N-dimethylformamide was treated with 30.0 mg (0.243 mmol) of ethyl acetimidate hydrochloride and 127 μL (0.729 mmol) of N,N-diisopropylethylamine and the mixture stirred for 20 h at ambient temperature. 1 N NaOH (10 mL) was added and the mixture extracted with ethyl acetate (3 x 10 mL). The combined extracts were washed with 10 mL of brine-1 N NaOH (9:1), dried (Na_2SO_4) and concentrated to 88 mg of a pale yellow resin. The above residue in 1.0 mL of anhydrous dichloromethane was treated with 101 μL (0.405 mmol) of 4 M HCl in dioxane and the solution concentrated *in vacuo* to a pale yellow resin. Concentration four more times from 2.0 mL of dichloromethane and placement under vacuum (0.5 torr/3 h) afforded 77.0 mg (91%) of a hard off-white foam. Mass spectrum (MALDI-TOF, α-cyano-4-hydroxy-cinnamic acid matrix) calcd. for $C_{23}H_{34}N_4O_3S$: 447.2 (M + H). Found: 447.3.

Example 4

N-Benzyl-N-[[[3-(1-acetimidoyl)piperidin-4-yl]methylamino]phenyl]benzene sulfonamide

a) ***N-(3-nitrophenyl)benzenesulfonamide***

To 6.17 g (44.7 mmol) of 3-nitroaniline and 8.41 mL (48.2 mmol) of N,N-diisopropylethylamine in 150 mL of anhydrous diethyl ether was added 5.14 mL (40.2 mmol) of benzenesulfonyl chloride. The mixture was heated to reflux under nitrogen with stirring for 16 h, cooled and the resulting two-phase mixture scratched to crystallize the insoluble oil. After decanting the ether layer, the

derived solid was dissolved in 300 mL of dichloromethane and the solution washed with 2 N HCl (3 x 200 mL), saturated $NaHCO_3$ (200 mL), brine (200 mL), dried (Na_2SO_4) and concentrated to give 9.62 g (86%) of the title compound as a light tan solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.96 (m, 2 H), 7.86 (m, 2 H), 7.41-7.63 (m, 5 H), and 7.30 (br s, 1 H). Mass spectrum (MALDI-TOF, gentisic acid matrix) calcd. for $C_{12}H_{10}N_2O_4S$: 301.0 (M + Na). Found: 301.1.

b) N-Benzyl-N-(3-nitrophenyl)benzenesulfonamide

To 6.00 g (21.6 mmol) of N-(3-nitrophenyl)benzenesulfonamide, as prepared in preceding step, in 15 mL of anhydrous N,N-dimethylformamide under nitrogen was added 4.48 g (32.4 mmol) of powdered anhydrous potassium carbonate and 2.83 mL (23.8 mmol) of benzyl bromide. After stirring for 3.5 h, the mixture was partitioned between 200 mL of ethyl acetate and 250 mL of water. The aqueous layer was extracted with 50 mL of ethyl acetate and the combined organic phases washed with 1 M K_2CO_3 (2 x 100 mL). Hexane (50 mL) was added to the organic phase which was then washed with water (3 x 150 mL), brine (100 mL), dried (Na_2SO_4) and concentrated to give 8.2 g of a crystalline yellow solid. Recrystallization from ethyl acetate-hexane afforded 7.45 g (94%) of the title compound as cream-colored crystals. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.06 (d, 1 H, J = 7.4 Hz), 7.76 (s, 1 H), 7.64 - 7.67 (m, 3 H), 7.51 - 7.56 (m, 2 H), 7.38 - 7.46 (m, 2 H), 7.21 (s, 5 H), and 4.77 (s, 2 H). Mass spectrum (MALDI-TOF, gentisic acid matrix) calcd. for $C_{19}H_{16}N_2O_4S$: 369.1 (M + H), 391.1 (M + Na), 407.0 (M + K). Found: 368.8, 391.3, 407.4.

c) N-Benzyl-N-(3-aminophenyl)benzenesulfonamide

To 3.01 g (8.17 mmol) of N-benzyl-N-(3-nitrophenyl)benzenesulfonamide, as prepared in preceding step, in 60 mL of methanol-tetrahydrofuran (1:1) was added 200 mg of 10 % palladium on carbon. After stirring the mixture under a balloon of hydrogen for 1.7 h, an additional 200 mg of 10 % palladium on carbon

was added and stirring was continued for another 2.5 h. Filtration (Celite) and concentration afforded a dark green resin which was dissolved in 40 mL of ethyl acetate-hexane (1:1), refiltered (Celite) and concentrated to afford 2.9 g of a yellow solid. Recrystallization from ethyl acetate-ether afforded 2.21 g (80%) of the title compound as a light orange crystalline powder. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.68 - 7.71 (m, 2 H), 7.56 - 7.62 (m, 1 H), 7.46 - 7.51 (m, 2 H), 7.18 - 7.2 (m, 5 H), 6.97 (t, 1 H, J = 8.0 Hz), 6.58 (dd, 1 H, J = 8.0, 1.6 Hz), 6.47 (t, 1 H, J = 2.1 Hz), 6.32 (dd, 1 H, J = 8.0, 1.3 Hz), and 4.70 (s, 1 H). Mass spectrum (MALDI-TOF, gentisic acid matrix) calcd. for $C_{19}H_{18}N_2O_2S$: 339.1 (M + H), 361.1 (M + Na). Found: 339.5, 361.5.

*d) N-Benzyl-N-[[3-(N-*tert*-butoxycarbonylpiperidin-4-yl)carbonylamino]-phenyl]benzenesulfonamide*

To 149 mg (0.650 mmol) of N-*tert*-butoxycarbonylisonipecotic acid, as prepared in step (a) in Example 1, and 287 mg (0.650 mmol) of Castro's Reagent (benzotriazole-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate, BOP) in 1.5 mL of anhydrous N,N-dimethylformamide was added 155 μL (0.887 mmol) of N,N-diisopropylethylamine and the mixture stirred under nitrogen for 5 min. A solution of 200 mg (0.591 mmol) of N-benzyl-N-(3-aminophenyl) benzenesulfonamide, as prepared in preceding step, in 0.5 mL of N,N-dimethylformamide was added. After stirring for 16 h, 10 mL of saturated $NaHCO_3$ was added. The mixture was partitioned between 25 mL each of ethyl acetate and water. The organic layer was washed with 10 % citric acid (2 x 20 mL), brine (20 mL) and dried (Na_2SO_4). Concentration afforded 360 mg of a yellow resin which was chromatographed on a Waters Associates 10 g silica Sep-Pak SPE column. Elution with a gradient of 5-10 % ethyl acetate-dichloromethane afforded 268 mg (82 %) of the title compound as a white foam. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.56 - 7.66 (m, 4 H), 7.47 (m, 2 H), 7.09 - 7.22 (m, 8 H), 6.60 (br d, 1 H, J = 8.0 Hz), 4.70 (s, 2 H), 4.14 (br s, 2 H), 2.74 (br t, 2 H, J = 12 Hz), 2.24-2.34 m, 1 H), 1.84 (br s, 1 H), 1.81 (br s, 1 H), 1.69 (td, 2

H, J = 12.2, 4.1 Hz), and 1.44 (s, 9 H). Mass spectrum (MALDI-TOF, gentisic acid matrix) calcd. for $C_{30}H_{35}N_3O_5S$: 450.6 (M - BOC + 2 H). Found: 450.3.

*e) N-Benzyl-N-[[[3-(1-*tert*-butoxycarbonyl)piperidin-4-yl]methylamino] phenyl]benzenesulfonamide*

To 404 μL (0.807 mmol) of 2 M lithium borohydride in tetrahydrofuran was added 1.0 mL of tetrahydrofuran followed by 204 μL (1.61 mmol) of chlorotrimethylsilane. After stirring for 4 min, 148 mg (0.269 mmol) of N-benzyl-N-[[3-(1-*tert*-butoxycarbonyl)piperidin-4-ylcarbonylamino]phenyl] benzenesulfonamide, as prepared in preceding step, in 2.0 mL of tetrahydrofuran was added and the mixture heated at 50°C under nitrogen for 2 h. After quenching the reaction with 0.16 mL of MeOH, 1.0 mL of 2 N NaOH was added, the mixture stirred for 10 min and then extracted with ethyl acetate (2 x 10 mL). The combined extracts were washed with brine, dried (Na_2SO_4) and concentrated to 150 mg of a pale yellow resin. Chromatography on a Waters Associates 10 g silica Sep-Pak SPE column eluting with 5% ethyl acetate - dichloromethane afforded 143 mg (99%) of the title compound as a colorless resin. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.70-7.74 (m, 2 H), 7.59 (m, 1 H), 7.48 (m, 2 H), 7.22 (m, 5 H), 6.95 (t, 1 H, J = 8.0 Hz), 6.40 (dd, 1 H, J = 8.1, 2.2 Hz), 6.25 (t, 1 H, J = 2.1 Hz), 6.17 (dd, 1 H, J = 7.2, 1.8 Hz), 4.70 (s, 2 H), 4.11 (br s, 2 H), 3.66 (br s, 1 H), 2.85 (br s, 2 H), 2.66 (t, 2 H, J = 13.3 Hz), 1.65 (d, 2 H, J = 13.3 Hz), 1.47 (s, 9 H), and 1.09 (m, 2 H). Mass spectrum (MALDI-TOF, gentisic acid matrix) calcd. for $C_{30}H_{37}N_3O_4S$: 435.6 (M - BOC + H). Found: 435.6.

f) N-Benzyl-N-[[[3-(1-acetimidoyl)piperidin-4-yl]methylamino]phenyl]-benzenesulfonamide

To 140 mg (0.261 mmol) of N-benzyl-N-[[[3-(1-*tert*-butoxycarbonyl) piperidin-4-yl]methylamino]phenyl]benzenesulfonamide, as prepared in preceding step, in 3.0 mL of anhydrous dichloromethane was added 0.75 mL of trifluoroacetic acid. After stirring for 15 min, the solution was concentrated and placed under vacuum (0.1 torr/1 h) to afford a colorless resin. This residue in 1.0

mL of anhydrous N,N-dimethylformamide was treated with 64.5 mg (0.522 mmol) of ethyl acetimidate hydrochloride and 182 μL (1.04 mmol) of N,N-diisopropylethylamine and the mixture stirred for 48 h. An additional 64.5 mg (0.522 mmol) of ethyl acetimidate hydrochloride and 91.0 μL (1.04 mmol) of N,N-diisopropylethylamine was added and the mixture stirred at 50°C for 20 h. To the mixture was added 20 mL of ethyl acetate and the solution washed with 0.1 N NaOH (2 x 20 mL). The combined aqueous layers were extracted with ethyl acetate (4 x 10 mL) and the five combined organic layers washed with 25 mL of brine and dried (Na_2SO_4) and concentrated to 91.4 mg of a pale yellow resin. This material was crystallized obtaining three crops from methanol-ethyl acetate and two crops from methanol-ethyl acetate-diethyl ether to afford 54.8 mg (44 %) of the title compound as a cream-colored powder. ^{1}H-NMR (300 MHz, CD_3OD) δ 7.65 - 7.72 (m, 3 H), 7.54 - 7.58 (m, 2 H), 7.18 - 7.24 (m, 5 H), 6.90 (t, 1 H, J = 8.1 Hz), 6.46 (dd, 1 H, J = 8.2, 2.0 Hz), 6.25 (t, 1 H, J = 2.1 Hz), 6.13 (d, 1 H, J = 7.8 Hz), 4.73 (s, 2 H), 4.02 (m, 2 H), 3.05-3.25 (m, 2 H), 2.88 (d, 2 H, J = 6.2 Hz), 2.31 (s, 3 H), 1.89 (m, 3 H), and 1.30 (m, 2 H). Mass spectrum (MALDI-TOF, α-cyano-4-hydroxycinnamic acid matrix) calcd. for $C_{27}H_{32}N_4O_2S$: 477.2 (M + H). Found: 477.2.

Example 5

3-Chlorobenzenesulfonic acid 3-[[(1-acetimidoyl)piperidin-4-yl]methoxy]-5-methylphenyl ester hydrochloride

a) 3-Chlorobenzenesulfonic acid 3-hydroxy-5-methylphenyl ester

Orcinol monohydrate (1.42 g, 10 mmol) and 3-chlorobenzenesulfonyl chloride (2.43 g, 11 mmol) were mixed in saturated $NaHCO_3$ (30 mL) and diethyl ether (30 mL). The biphasic mixture was stirred vigorously at room temperature for 2 days. After adding water (50 mL) to the mixture, the mixture was extracted with ethyl acetate (3 x 50 mL). The organic phase was then washed with brine (2 x 50 mL) and dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (2% ethyl acetate in

methylene chloride) to give the title compound as a pale-yellow liquid (2.08 g, 69%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.24 (s, 3 H), 5.32 (s, 1 H), 6.33 (t, 1 H, J = 2.2 Hz), 6.40 (s, 1 H), 6.57 (s, 1 H), 7.48 (t, 1 H, J = 8.0 Hz), 7.65 (m, 1 H), 7.73 (m, 1 H), and 7.86 (t, 1 H, J = 1.8 Hz).

*b) 3-Chlorobenzenesulfonic acid 3-[[N-(*tert*-butoxycarbonyl)piperidin-4-yl]methoxy]-5-methylphenyl ester*

Diethyl azodicarboxylate (349 mg, 2.0 mmol) was added to a solution of 3-chlorobenzenesulfonic acid 3-hydroxy-5-methylphenyl ester (600 mg, 2.0 mmol), as prepared in the preceding step, N-*tert*-butoxycarbonyl-4-piperidinemethanol (430 mg, 2.0 mmol), as prepared in step (b) of Example 1, and triphenylphosphine (525 mg, 2.0 mmol) in tetrahydrofuran (20 mL) at 0°C. The mixture was stirred at 0°C for 2 h and at room temperature for 3 h. The reaction was quenched with water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The organic phase was washed with saturated $NaHCO_3$ (2 x 50 mL), brine (2 x 50 mL) and dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (1:3 ethyl acetate/hexane) to give the title compound as a colorless liquid (800 mg, 81%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.24 (m, 2 H), 1.47 (s, 9 H), 1.75 (m, 2 H), 1.90 (m, 1 H), 2.25 (s, 3 H), 2.73 (t, 2 H, J = 12.5 Hz), 3.68 (d, 2 H, J = 3.1 Hz), 4.13 (m, 2 H), 6.34 (t, ^{1}H, J = 2.2 Hz), 6.39 (s, 1 H), 6.61 (s, 1 H), 7.49 (t, 1 H, J = 7.8 Hz), 7.63 (d, 1 H, J = 0.7 Hz), 7.75 (d, 1 H, J = 3.9 Hz), and 7.86 (t, 1 H, J = 1.8 Hz).

c) 3-Chlorobenzenesulfonic acid 3-[[(1-acetimidoyl)piperidin-4-yl]methoxy]-5-methylphenyl ester hydrochloride

3-Chlorobenzenesulfonic acid 3-[[N-(*tert*-butoxycarbonyl)piperidin-4-yl]methoxy]-5-methylphenyl ester (496 mg, 1.0 mmol), as prepared in the preceding step, was stirred with 4 N HCl in 1,4-dioxane (15 mL) at room temperature for 2 h. The solvent was removed *in vacuo*, and the residue was co-evaporated with methylene chloride several times to give the amine hydrochoride salt. The amine hydrochloride salt was then treated with

triethylamine (1.0 mL) and ethyl acetimidate hydrochloride (247 mg, 2.0 mmol) in N,N-dimethylformamide (10 mL) and stirred at room temperature overnight. The N,N-dimethylformamide was removed *in vacuo*. The residue was partitioned between methylene chloride (200 mL) and 10% K_2CO_3 (50 mL). The organic phase was washed with 10% K_2CO_3 (2 x 50 mL) and dried over K_2CO_3.. The solvent was removed *in vacuo*, the residue treated with HCl-methanol (30 mL), and then concentrated *in vacuo*. The residue was then purified by chromatography (15% methanol in methylene chloride) and crystallized (methanol - ethyl acetate) to give the title compound as white crystals (275 mg, 58 %). ^{1}H-NMR (300 MHz, DMSO-d_6) δ 1.34 (m, 2 H), 1.84 (d, 2 H, J = 7 Hz), 2.06 (m, 1 H), 2.22 (s, 3 H), 2.28 (s, 3 H), 3.16 (m, 2 H), 3.78 (d, 2 H, J = 3.1 Hz), 3.93 (d, 1 H, J = 6.5 Hz), 4.12 (d, 1 H, J = 6.5 Hz), 6.43 (t, 1 H, J = 2.1 Hz), 6.49 (s, 1 H), 6.77 (s, 1 H), 7.72 (t, 1 H, J = 7.5 Hz), 7.85 (t, 1 H, J = 1.4 Hz,), 7.92 (m, 2 H), 8.67 (br s, 1 H), and 9.24 (br s , 1 H). Mass spectrum (MALDI-TOF, sinapinic acid matrix) calcd. for $C_{21}H_{25}N_2O_4SCl$: 437.1 (M+ H). Found: 436.8.

Example 6

2-Chlorobenzenesulfonic acid 3-[(3-amidinophenyl)methoxy]-5-methylphenyl ester hydrochloride

a) 2-Chlorobenzenesulfonic acid 3-[(3-cyanophenyl)methoxy]-5-methylphenyl ester

Diethyl azodicarboxylate (349 mg, 2.0 mmol) was added to a solution of 2-chlorobenzenesulfonic acid 3-hydroxy-5-methylphenyl ester (900 mg, 3.0 mmol), as prepared in step (c) of Example 1, 3-cyanobenzyl alcohol (400 mg, 3.0 mmol; Yoon *et al., J. Org. Chem. 38*:2786-2792 (1973)), and triphenylphosphine (525 mg, 2.0 mmol) in tetrahydrofuran (20 mL) at 0°C. The mixture was stirred at 0°C for 2 h and at room temperature for 3 h. The reaction mixture was quenched with water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The organic phase was washed with saturated $NaHCO_3$ (2 x 50 mL), brine (2 x 50 mL) and dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue was

purified by flash column chromatography (2:1 ethyl acetate/hexane) to give the title compound as a white solid (1.10 g, 89%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.26 (s, 3 H), 4.99 (s, 2 H), 6.55 (t, 1 H, J = 2.3 Hz), 6.60 (t, 1 H, J = 0.7 Hz), 6.67 (t, 1 H, J = 0.7 Hz), 7.39 (m, 1 H), 7.50 (t, 1 H, J = 7.7 Hz), 7.61 (m, 5 H), and 7.96 (d, 1 H, J = 1.3 Hz).

b) 2-Chlorobenzenesulfonic acid 3-[(3-amidinophenyl)methoxy]-5-methylphenyl ester hydrochloride

To a solution of 2-chlorobenzenesulfonic acid 3-[(3-cyanophenyl) methoxy]-5-methylphenyl ester (207 mg, 0.5 mmol), as prepared in the preceding step, in methylene chloride (10 mL) was added 37% HCl in ethanol (10 mL) at 0°C. The mixture was allowed to stand at 0°C for 3 days. The solvent was evaporated *in vacuo* and the residue was co-evaporated with methylene chloride several times. The residue was dissolved in ethanol (10 mL) and ammonium carbonate (192 mg, 2.0 mmol) was added at 0°C. The mixture was stirred at room temperature overnight. Methylene chloride (150 mL) was added to the mixture. The methylene chloride solution was washed with 10% K_2CO_3 (2 x 50 mL) and dried over K_2CO_3. The solvent was removed *in vacuo*, HCl in methanol (30 mL) was added, and the solvent again removed *in vacuo*. The residue was purified by flash chromatography (10% methanol in methylene chloride) to give the title compound as a white solid (112 mg, 48%). ^{1}H-NMR (300 MHz, DMSO-d_6) δ 2.23 (s, 3 H), 5.11 (s, 2 H), 6.54 (s, 1 H), 6.56 (s, 1 H), 6.88 (s, 1 H), 7.58 (t, 1 H, J = 6.5 Hz), 7.61 (t, 1 H, J = 12.2 Hz), 7.66 (d, 1 H, J = 3.9 Hz), 7.73 - 7.95 (m, 5 H), and 9.40 (br s, 4 H). Mass spectrum (MALDI-TOF, sinapinic acid matrix) calcd. for $C_{21}H_{19}N_2O_4SCl$: 431.1 (M + H), 453.1 (M + Na). Found: 431.0, 452.9.

Example 7

2-Chlorobenzenesulfonic acid 3-[[3-(N-hydroxy)amidinophenyl]methoxy]-5-methylphenyl ester hydrochloride

To a solution of 2-chlorobenzenesulfonic acid 3-[(3-cyanophenyl) methoxy]-5-methylphenyl ester (207 mg, 0.5 mmol), as prepared in step (a) of the Example 6, in methylene chloride (10 mL) was added 37% HCl in ethanol (10 mL) at 0°C. The mixture was allowed to stand at 0°C for 3 days. The solvent was removed *in vacuo* and the residue was co-evaporated with methylene chloride several times. The residue was dissolved in ethanol (10 mL) and then treated with hydroxylamine hydrochloride (140 mg, 2.0 mmol) and Na_2CO_3 (106 mg, 1.0 mmol). The reaction mixture was stirred at room temperature for 2 days. Methylene chloride (150 mL) was added to the mixture, washed with 10% K_2CO_3 (2 x 50 mL), and dried over K_2CO_3. The solvent was removed *in vacuo*, HCl in methanol (30 mL) added and the solvent removed *in vacuo*. The residue was purified by flash chromatography (1:1 ethyl acetate/methylene chloride) to give the title compound as a white foam (95 mg, 39%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.25 (s, 3 H), 4.89 (br s, 1 H), 4.98 (d, 2 H, J = 10.7 Hz), 5.58 (br s, 1 H), 6.15 (br s ,1 H), 7.33-7.64 (m, 6 H), 7.76-7.83 (m, 1 H), and 7.92 (d, 1 H, J = 4.0 Hz). Mass spectrum (MALDI-TOF, sinapinic acid matrix) calcd. for $C_{21}H_{19}N_2O_5SCl$: 447.1 (M + H), 469.1 (M + Na). Found: 447.1, 469.2.

Example 8

2,3-Dichlorobenzenesulfonic acid 3-[[(1-acetimidoyl)piperidin-4-yl]methoxy]-5-methylphenyl ester hydrochloride

a) 2,3-Dichlorobenzenesulfonic acid 3-hydroxy-5-methylphenyl ester

A solution of orcinol monohydrate (0.71 g, 5.0 mmol) and 2,3-dichlorobenzenesulfonyl chloride (1.23 g, 5.0 mmol) in saturated $NaHCO_3$ (20 mL) and diethyl ether (20 mL was stirred at room temperature for 2 days. The reaction mixture was quenched with water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The organic phase was washed with brine (2 x 50 mL) and dried over Na_2SO_4. The solvent was evaporated *in vacuo* and the residue was purified by flash column chromatography (methylene chloride to 2% ethyl acetate in methylene chloride) to give the title compound as a pale yellow oil (0.89 g, 55%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.24 (s, 3 H), 5.23 (s, 1 H), 6.43 (t, 1 H, J = 2.2 Hz), 6.54 (d, 2 H, J = 1.1 Hz), 7.34 (t, 1 H, J = 8.1 Hz), 7.75 (dd, 1 H, J = 0.8, 4.0 Hz), and 7.91 (dd, 1 H, J = 0.8, 4.0 Hz).

b) 2,3-Dichlorobenzenesulfonic acid 3-[[N-(tert-butoxycarbonyl)piperidin-4-yl]methoxy]-5-methylphenyl ester

Diethyl azodicarboxylate (349 mg, 2.0 mmol) was added to a solution of 2,3-dichlorobenzenesulfonic acid 3-hydroxy-5-methylphenyl ester (644 mg, 2.0 mmol), as prepared in the preceding step, N-*tert*-butoxylcarbonyl-4-piperidinemethanol (430 mg, 2.0 mmol), as prepared in step (b) of Example 1, and triphenylphosphine (525 mg, 2.0 mmol) in tetrahydrofuran (20 mL) at 0°C. The mixture was stirred at 0°C for 2 h and at room temperature for 3 h. The reaction mixture was quenched with water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The organic phase was washed with saturated $NaHCO_3$ (2 x 50 mL), brine (2 x 50 mL) and dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (1:3 ethyl acetate/hexane) to give the title compound as a colorless syrup (930 mg, 88%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.26 (m, 2 H), 1.47 (s, 9 H), 1.75 (m, 2 H), 1.90

(m, 1 H), 2.25 (s, 3 H), 2.73 (t, 2 H, J = 2.0 Hz), 3.68 (d, 2 H, J = 3.2 Hz), 4.13 (m, 2 H), 6.47 (d, 1 H, J = 1.1 Hz), 6.53 (d, 1 H, J = 0.4 Hz), 6.59 (s, 1 H), 7.34 (t, 1 H, J = 8.2 Hz), 7.75 (m, 1 H), and 7.92 (m, 1 H).

c) 2,3-Dichlorobenzenesulfonic acid 3-[[(1-acetimidoyl)piperidin-4-yl]methoxy]-5-methylphenyl ester hydrochloride

2,3-Dichlorobenzenesulfonic acid 3-[[N-(*tert*-butoxycarbonyl)piperidin-4-yl]methoxy]-5-methylphenyl ester (530 mg, 1.0 mmol), as prepared in the preceding step, was stirred with 4 N HCl in 1,4-dioxane (10 mL) at room temperature for 2 h. The solvent was evaporated *in vacuo*, the residue was co-evaporated with methylene chloride several times to give the amine HCl salt. Triethylamine (0.5 mL) and ethyl acetimidate hydrochloride (247 mg, 2.0 mmol) were added to a solution of the above amine in N,N-dimethylformamide (10 mL) and the reaction mixture was stirred at room temperature for 2 days. The N,N-dimethylformamide was removed *in vacuo* and the residue was partitioned between methylene chloride (200 mL) and 10% K_2CO_3 (50 mL). The organic phase was washed with 10% K_2CO_3 (2 x 50 mL) and dried over K_2CO_3. After removing the solvent *in vacuo*, HCl-methanol (30 mL) was added and the solution concentrated. The residue was then crystallized from methanol-ethyl acetate to give the title compound as white crystals (420 mg, 83%). ^{1}H-NMR (300 MHz, DMSO-d_6) δ 1.34 (m, 2 H), 1.84 (d, 1 H, J = 8.6 Hz), 2.04 (m, 1 H), 2.22 (s, 3 H), 2.29 (s, 3 H), 3.16 (m, 2 H), 3.78 (d, 2 H, J = 3.2 Hz), 3.92 (d, 1 H, J = 7.0 Hz), 4.15 (d, 1 H, J = 7.0 Hz), 6.46 (t, 1 H, J = 2.2 Hz), 6.52 (s, 1 H), 6.77 (s, 1 H), 7.62 (t, 1 H, J = 8.1 Hz), 7.96 (d, 1 H, J = 4.0 Hz), 8.14 (d, 1 H, J = 4.0 Hz), 8.74 (br s, 1 H), and 9.32 (br s, 1 H). Mass spectrum (MALDI-TOF, sinapinic acid matrix) calcd. for $C_{21}H_{24}N_2O_4SCl_2$: 471.1 (M+ H). Found: 471.1.

Example 9

2-Chloro-N-[[3-[(1-acetimidoyl)piperidin-4-yl]methoxy]-5-trifluoromethylphenyl]benzenesulfonamide hydrochloride

a) 3-(Trifluoromethyl)-5-nitrophenol

3-Methoxy-5-nitrobenzotrifluoride (5 g, 23 mmol) was dissolved in anhydrous methylene chloride (100 mL) and cooled to -80°C under a nitrogen atmosphere. To this solution was added via dropping funnel a 1 M solution of BBr3 in methylene chloride (68 mL, 68 mmol). This solution was allowed to warm to room temperature and stirred for 3 days. Water was slowly added to the mixture and mixed well to quench the excess BBr_3. To this mixture ether (500 mL) was added. The organic layer was separated and extracted with 2 N NaOH (240 mL). The alkaline extract was neutralized with dilute HCl and extracted with diethyl ether (3 x 300 mL). The ether extracts were combined, washed with saturated NaCl and dried over anhydrous $MgSO_4$. Evaporation of diethyl ether gave a brownish yellow oil which was chromatographed on a silica column to give 1.6 g (34%) of a yellow solid. ^{1}H-NMR ($CDCl_3$/CD_3OD; 300 MHz) δ 7.38 - 7.40 (m, 1 H), 7.82 (t, 1 H, J = 2.2 Hz), and 7.95 - 7.96 (m, 1 H).

b) 3-[[1-(Tert-butoxycarbonyl)piperidin-4-yl]methoxy]-5-nitrobenzotrifluoride

The title compound was synthesized by treating 3-(trifluoromethyl)-5-nitrophenol (1.47 g, 7.1 mmol), as prepared in the preceding step, in a manner analogous to step (d) of Example 1 to give 2.17 g (76%) as an oil. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.24 - 1.38 (m, 2 H), 1.48 (s, 9 H), 1.82 - 1.87 (m, 2 H), 1.96 - 2.10 (m, 1 H), 2.73 - 2.81 (m, 2 H), 3.93 (d, 2 H, J = 6.3 Hz), 4.09 - 4.21 (m, 2 H), 7.45 - 7.46 (m, 1 H), 7.89 (t, 1 H, J = 2.2 Hz), and 8.07 - 8.08 (m, 1 H).

c) ***2-Chloro-N-[[3-[(1-*tert*-butoxycarbonyl)piperidin-4-yl]methoxy]-5-trifluoromethylphenyl]benzenesulfonamide***

To a methanolic solution of 3-[(piperidin-4-yl)methoxy]-5-nitrobenzotrifluoride (2.17 g in 200 mL), as prepared in the preceding step, and 10% Pd/C (300 mg) was stirred under a hydrogen atmosphere for 20 h. The catalyst was removed by filtration and the methanol was evaporated to give a white foam. The foam was dried under high vacuum overnight and dissolved in anhydrous methylene chloride (10 mL). The methylene chloride solution was cooled in an ice bath under a nitrogen atmosphere and 2-chlorobenzenesulfonyl chloride (1.17 g, 5.50 mmol) and N-methylmorpholine (6.05 mmol) were added and the mixture allowed to warm to room temperature. The mixture was stirred for 2 days at which time N-methylmorpholine (200 μL) was added and the mixture heated to reflux for 3 h. The methylene chloride solution was diluted with another 50 mL of methylene chloride and extracted with 10 % citric acid and saturated $NaHCO_3$. The organic layer was separated, washed with saturated NaCl and dried over anhydrous $MgSO_4$. Evaporation of the methylene chloride gave an oil which was chromatographed on a silica column to give 2.4 g (80 %) of a white solid. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.17 - 1.31 (m, 2 H), 1.47 (s, 9 H), 1.75 - 1.80 (m, 2 H), 1.83 - 1.98 (m, 1 H), 2.69 - 2.78 (m, 2 H), 3.74 (d, 1 H, J = 6.2 Hz), 4.09 - 4.16 (m, 2 H), 6.81 (b s, 1 H), 6.87 - 6.89 (m, 1 H), 6.90 (br s, 1 H), 7.34 - 7.43 (m, 2 H), 7.50 - 7.54 (m, 2 H), and 8.05 - 8.08 (m, 1 H).

d) ***2-Chloro-N-[[3-[piperidin-4-yl]methoxy]-5-trifluoromethylphenyl]-benzenesulfonamide trifluoroacetate***

2-Chloro-N-[[3-[(1-*tert*-butoxycarbonyl)piperidin-4-yl]methoxy]-5-trifluoromethylphenyl]benzenesulfonamide (0.33 g, 0.64 mmol) was treated with 25% trifluoroacetic acid in methylene chloride (5 mL) at ambient temperature for 0.5 h. The reaction mixture was evaporated to dryness and azeotroped with acetonitrile (3 times). The residue was triturated with hexane (twice) and diethyl ether, then placed under high vacuum overnight. Mass spectrum (MALDI-TOF, gentisic acid matrix) calcd. for $C_{19}H_{20}N_2O_3SClF_3$: 449.1 (M+H). Found: 449.8.

e) 2-Chloro-N-[[3-[(1-acetimidoyl)piperidin-4-yl]methoxy]-5-trifluoromethylphenyl]benzenesulfonamide hydrochloride

2-Chloro-N-[[3-[piperidin-4-yl]methoxy]-5-trifluoromethylphenyl] benzenesulfonamide trifluoroacetate from step (d) above was dissolved in N,N-dimethylformamide (10 mL) and treated with ethyl acetimidate hydrochloride (0.16 g, 1.28 mmol) and triethylamine (0.27 mL, 1.92 mmol). The reaction mixture was stirred at ambient temperature overnight. The reaction mixture was diluted with water (cloud point) to initiate crystallization. The solid precipitate was collected by filtration and washed with water. The solid was dried under high vacuum overnight to give 0.218 g of the title compound. ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 1.33 (m, 2 H), 1.84 (d, 3 H), 2.04 - 2.12 (m, 1 H), 2.26 (s, 3 H), 3.10 - 3.33 (m, 2 H), 3.74 (d, 2 H), 3.91 - 4.02 (m, 2 H), 6.32 (br s, 1 H), 6.57 (s, 1 H), 6.67 (br s, 1 H), 7.28 - 7.42 (m, 3 H), 7.93 (dd, 1 H), 8.48 (br s, 1 H), and 9.04 (br s, 1 H).

Example 10

2-Chloro-N-(5-carboxypentyl)-N-[[3-[(1-acetimidoyl)piperidin-4-yl]methoxy]-5-trifluoromethylphenyl]benzenesulfonamide

a) 2-Chloro-N-(5-ethoxycarbonylpentyl)-N-[[3-[(1-tert-butoxycarbonyl)piperidin-4-yl]methoxy]-5-trifluoromethylphenyl] benzenesulfonamide

A solution of 2-chloro-N-[[3-[(1-*tert*-butoxycarbonyl)piperidin-4-yl]methoxy]-5-trifluoromethylphenyl]benzenesulfonamide (0.6 g, 1.1 mmol) in N,N-dimethylformamide (10 mL) was treated with potassium carbonate (0.15 g, 1.1 mmol) and ethyl 6-bromohexanoate (0.20 mL, 1.1 mmol). The reaction was warmed at 50-60°C for 2 days. The reaction mixture was diluted with water, neutralized with 5% hydrochloric acid, and extracted with ethyl acetate (3 x). The ethyl acetate was washed with brine, dried (Na_2SO_4), and evaporated to dryness. The residue was purified by solid phase extraction using a 10 g Sep-Pak column (Waters Associates) and elution with 20% ethyl acetate - hexanes to give 0.70 g (92% yield). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.26-1.43 (m, 2H), 1.44 (s, 9 H),

1.45 - 1.96 (m, 9 H), 2.24 (t, 2 H), 2.72 (br t, 2 H), 3.73 - 3.81 (m, 4 H), 4.05 - 4.16 (m, 4 H), 6.89 (br s, 1 H), 6.96 (m, 2 H), 7.24 (dt, 1 H), 7.40 - 7.50 (m, 2 H), and 7.81 (dd, 1 H).

*b) 2-Chloro-N-(5-carboxypentyl)-N-[[3-[(1-*tert*-butoxycarbonyl)piperidin-4-yl]methoxy]-5-trifluoromethylphenyl] benzenesulfonamide*

A solution of 2-chloro-N-(5-ethoxycarbonylpentyl)-N-[[3-[(1-*tert*-butoxycarbonyl)piperidin-4-yl]methoxy]-5-trifluoromethylphenyl] benzenesulfonamide, as prepared in the preceding step, (0.70 g, 1 mmol) was dissolved in a 4:1 dioxane/water mixture (12 mL) and treated with lithium hydroxide monohydrate (0.042 g, 1 mmol). The reaction mixture was allowed to stir at ambient temperature for 2 days, then warmed at 50°C overnight. An additional 0.042 g of lithium hydroxide monohydrate was added and the temperature maintained at 50°C for 5 h. The reaction mixture was extracted with methylene chloride. The aqueous layer was acidified with 5% hydrochloric acid and extracted with methylene chloride. The combined methylene chloride extracts were washed with brine, dried (Na_2SO_4), and evaporated to dryness to give 0.68 g (quantitative) of the title compound. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.20 - 2.00 (m, 20 H), 2.32 (t, 2 H), 2.75 (br t, 2 H), 3.76 - 3.84 (m, 4 H), 4.16 (m, 2 H), 6.92 (br s, 1 H), 6.99 (m, 2 H), 7.28 (dt, 1 H), 7.44 (dd, 1 H), 7.49 (dd, 1 H), and 7.84 (dd, 1 H).

c) 2-Chloro-N-(5-carboxypentyl)-N-[[3-[(1-acetimidoyl)piperidin-4-yl]methoxy]-5-trifluoromethylphenyl]benzenesulfonamide

A solution of 2-chloro-N-(5-carboxypentyl)-N-[[3-[(1-*tert*-butoxycarbonyl)piperidin-4-yl]methoxy]-5-trifluoromethylphenyl] benzenesulfonamide, as prepared in the preceding step, (0.68 g, 1 mmol) in 25% trifluoroacetic acid in methylene chloride (15 mL) was stirred at ambient temperature for 0.5 h. The reaction mixture was evaporated to dryness, azeotroped with acetonitrile (3 times), and triturated with hexanes (twice) and 2:1 hexanes/diethyl ether (twice). The residue was placed under high vacuum to give

0.6 g of 2-chloro-N-(5-carboxypentyl)-N-[[3-[piperidin-4-yl]methoxy]-5-trifluoromethylphenyl]benzenesulfonamide trifluoroacetate.

A solution of 2-chloro-N-(5-carboxypentyl)-N-[[3-[piperidin-4-yl]methoxy]-5-trifluoromethylphenyl]benzenesulfonamide trifluoroacetate (0.3 g, 0.5 mmol) in N,N-dimethylformamide (10 mL) was treated with triethylamine (0.21 mL, 1.5 mmol) and ethyl acetimidate hydrochloride (0.13 g, 1 mmol) at ambient temperature. The reaction mixture was diluted with water to produce an oily gum. The aqueous layer was decanted and the oily gum was treated with a small amount of methanol and diluted with water to initiate crystallization. The solid was collected by filtration, washed with water, and dried under high vacuum to give 7.4 mg of the title compounds as a white solid. ^{1}H-NMR ($CDCl_3$/TFA, 300 MHz) δ 1.26 - 2.44 (m, 16 H), 2.9 - 3.4 (m, 2 H), 3.62 - 4.55 (m, 6 H), 6.90 (d, 1 H), 7.04 - 7.08 (m, 2 H), 7.33 (dt, 1 H), 7.55 (m, 2 H), and 7.84 (d, 1 H). Mass spectrum (MALDI-TOF, α-cyano-4-hydroxycinnamic acid matrix) calcd. for $C_{27}H_{33}N_3O_5SClF_3$: 604.2 (M+H). Found: 604.3.

Example 11

1-(5-(N,N-Dimethylamino)naphthalenesulfonic acid 3-[[(1-acetimidoyl)piperidin-3-yl]methoxy]-5-methoxyphenyl ester hydrochloride

a) 1-(5-(N,N-Dimethylamino)naphthalenesulfonic acid 3-hydroxy-5-methoxyphenyl ester

A biphasic solution of 1.08 g (7.78 mmol) of 5-methoxyresorcinol, 2.10 g (7.78 mmol) of dansyl chloride, 30 mL of diethyl ether, and 30 mL of saturated sodium bicarbonate was vigorously stirred at ambient temperature overnight. The reaction mixture was quenched with pH 7 buffer, extracted into diethyl ether, dried ($MgSO_4$), and purified by flash chromatography (1-2% ether/methylene chloride) to provide 605.5 mg (21% yield) of the title compound was a bright yellow powder. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.59 (d, 1 H, J = 8.5 Hz), 8.43 (d, 1 H, J = 8 Hz), 8.12 (dd, 1 H, J = 1, 7 Hz), 7.66 (dd, 1 H, J = 8, 8.5 hz), 7.46 (dd, 1 H, J = 7.4, 8.5 Hz), 7.25 (d, 1 H, J = 7.5 Hz), 6.20 (t, 1 H, J = 2.2 Hz),

6.04 (t, J = 2.2 Hz), 6.01 (t, 1 H, J = 2.2 Hz), 5.62 (br s, 1 H), 3.55 (s, 3 H), and 2.99 (s, 6 H). Mass spectrum (MALDI-TOF; α-cyano-4-hydroxycinnamic acid matrix) calcd. for $C_{19}H_{19}NO_5S$: 374.1 (M + H), 396.1 (M + Na). Found: 373.7, 395.7.

b) N-(tert-Butoxycarbonyl)-3-piperidinemethanol

To a solution of 3-piperidinemethanol (4.60 g, 40 mmol) and triethylamine (6 mL) in 1,4-dioxane (100 mL) was added slowly di-*tert*-butyl dicarbonate (8.72 g, 40 mmol). After stirring at room temperature for 2 h, the solvent was removed *in vacuo* and the residue purified by flash column chromatography (2:1 hexane/ethyl acetate) to give the title compound as white solid (7.81 g, 91%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.25-1.39 (m, 2 H), 1.46 (s, 9 H), 1.60-1.81 (m, 3 H), 1.94 (br s, 1 H), 2.98-3.08 (m, 2 H), 3.51 (d, 2 H), and 3.66-3.77 (m, 2 H).

c) 1-(5-(N,N-Dimethylamino)naphthalenesulfonic acid 3-[[N-(tert-butoxycarbonyl)piperidin-3-yl]methoxy]-5-methoxyphenyl ester

To a solution of 379 mg (1.05 mmol) of 1-(5-(N,N-dimethylamino) naphthalenesulfonic acid 3-hydroxy-5-methoxyphenyl ester as prepared in Step a of this Example, in tetrahydrofuran (10 mL) containing 275 mg (0.347 mmol) of N-(*tert*-butoxycarbonyl)-3-piperidinemethanol, as prepared in the preceding step, 358 mg (1.36 mmol) of triphenylphosphine, and 350 μL (3.18 mmol) of N-methylmorpholine was added 215 μL (1.36 mmol) of diethyl azodicarboxylate. The reaction mixture was stirred at ambient temperature for 1 h, quenched with pH 7 buffer, extracted into diethyl ether, dried ($MgSO_4$), and concentrated *in vacuo*. The product was purified by flash chromatography to provide 245.7 mg (38% yield) of the title compound as a yellow foam. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.60 (d, 1 H, J = 8.6 Hz), 8.45 (d, 1 H, J = 8.7 Hz), 8.13 (dd, 1 H, J = 1.2, 7.3 Hz), 7.67 (dd, 1 H), 7.47 (dd, 1 H, J = 7.4, 8.5 Hz), 7.24 (1 H, J = 8.5 Hz), 6.24 (t, 1 H, J = 2.2 Hz), 6.10 (t, 1 H, J = 1.9 Hz), 5.99 (t, 1 H, J = 2.1 Hz), 3.88 (br d, 2 H), 3.55 (s, 3 H), 2.90 (s, 6 H), 1.58 (s, 3 H), and 1.44 (s, 9 H). Mass

spectrum (MALDI-TOF; α-cyano-4-hydroxycinnamic acid matrix) calcd. for $C_{39}H_{38}N_2O_7S$: 593.2 (M + Na). Found: 593.0.

d) 1-(5-(N,N-Dimethylamino)naphthalenesulfonic acid 3-[(piperidin-3-yl)methoxy]-5-methoxyphenyl ester hydrochloride

To 245 mg of 1-(5-(N,N-dimethylamino)naphthalenesulfonic acid 3-[[N-(*tert*-butoxycarbonyl)piperidin-3-yl]methoxy]-5-methoxyphenyl ester, as prepared in the preceding step, in methylene chloride (1 mL) was added 500 μL of 4 N HCl in dioxane. The reaction mixture was stirred for 1 h. The reaction mixture was treated with another 1 mL of 4 N HCl in dioxane and stirring was continued for another 1 h. The reaction mixture was concentrated repeatedly from diethyl ether/methanol/hexane to afford 237.7 mg of the title compound as a hardened foam. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.19 (d, 1 H), 9.03 (q, 1 H), 8.72 (d, 1 H, J = 8.5 Hz), 8.35 (d, 1 H, J = 8.6 Hz), 8.17 (dd, 1 H, J = 1.1, 7.3 Hz), 7.84 (t, 1 H, J = 7.9 Hz), 7.69 (dd, 1 H, J = 7.6, 8.5 Hz), 7.51 (1, H, J = 7.7 Hz), 6.41 (t, 1 H, J = 2.2 Hz), 6.08 (t, 1 H, J = 2.1 Hz), 5.92 (t, 1 H, J = 2.1 Hz), 3.57 - 3.76 (m, 2 H), 3.53 (s, 3 H), 3.2 - 3.23 (m, 2 H), 2.94 (s, 6 H), 2.58 - 2.8 (m, 2 H), 2.14 (br s, 1 H), 1.62 - 1.80 (m, 2 H), 1.17 - 1.3 (m, 1 H). Mass spectrum (MALDI-TOF; α-cyano-4-hydroxycinnamic acid matrix) calcd. for $C_{25}H_{30}N_2O_5S$: 471.2 (M + H), 493.2 (M + Na). Found: 470.9, 492.9.

e) 1-(5-(N,N-Dimethylamino)naphthalenesulfonic acid 3-[[1-acetimidoyl)piperidin-3-yl]methoxy]-5-methoxyphenyl ester hydrochloride

To a solution of 204.7 mg of 1-(5-(N,N-dimethylamino) naphthalenesulfonic acid 3-[(piperidin-3-yl)methoxy]-5-methoxyphenyl ester hydrochloride, as prepared in the preceding step in 2 mL of N,N-dimethylformamide containing 380 μL (3.42 mmol) of N,N-diisopropylethylamine was added 190 mg (1.54 mmol) of ethyl acetimidate hydrochloride. The reaction mixture was stirred at ambient temperature for 2 days. The solvent was removed *in vacuo* and the residue was quenched with 2 N sodium hydroxide. The reaction

mixture was extracted into methylene chloride, dried (K_2CO_3), and concentrated *in vacuo*. The residue was dissolved in methylene chloride (1 mL), treated with 500 μL of glacial acetic acid and then flash chromatographed (methylene chloride/methanol/glacial acetic acid (92.6:6.5:0.9) to afford the acetic acid salt of the product as a gum. The gum was dissolved in methylene chloride and treated with 1 N sodium hydroxide. The organic phase was dried (K_2CO_3) and concentrated *in vacuo*. The residue was dissolved in methylene chloride, treated with 1 mL of 4 N HCl in dioxane and repeatedly concentrated from diethyl ether/methylene chloride/hexane to give 177 mg of the title compound as a pale yellow powder. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.37 and 9.33 (br s, 1 H), 8.78 (s, 1 H), 8.71 (d, 1 H, J = 7.8 Hz), 8.34 (d, 1 H, J = 8.6 Hz), 8.14 - 8.18 (m, 2 H), 7.84 (t, 1 H, J = 7.8 Hz), 7.69 (dt, 1 H, J = 1.1, 8.8 Hz), 7.49 (d, 1 H, J = 7.6 Hz), 6.45 and 6.42 (t, 1 H), 6.16 and 6.10 (t, 1 H), 5.92 and 5.89 (t, 1 H), 3.53 (s, 3 H), 2.92 (t, 6 H), 2.28 and 2.22 (s, 3 H). Mass spectrum (MALDI-TOF; α-cyano-4-hydroxycinnamic acid matrix) calcd. for $C_{27}H_{33}N_3O_5S$: 512.2 (M + H). Found: 511.5.

Example 12

2-Chlorobenzenesulfonic acid 1-[[(1-acetimidoyl)piperidin-4-yl]methoxy]naphthalen-3-yl ester acetic acid salt

a) 2-Chlorobenzenesulfonic acid 1-hydroxynaphthalen-3-yl ester

At 0°C to 1.0 g (6.24 mmol) of 1,3-naphthalenediol in tetrahydrofuran (20 mL) containing 1.5 mL of 2,6-lutidine was added 1.35 g (6.40 mmol) of 2-chlorobenzenesulfonyl chloride. The reaction mixture was stirred to ambient temperature overnight, quenched with 3 N hydrochloric acid, extracted into methylene chloride, and dried ($MgSO_4$). Purification by flash chromatography (2% ethyl acetate/methylene chloride) gave 277 mg (13% yield) of the title compound as a colorless solid. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.75 (s, 1 H), 8.06 (d, 1 H, J = 1.7 Hz), 7.78 - 7.95 (m, 4 H), 7.43 - 7.57 (m, 3 H), 7.11 (d, 1 H, J = 2 Hz), and 6.63 (d, 1 H, J = 2 Hz).

b) ***2-Chlorobenzenesulfonic acid 1-[[1-N-(tert-butoxycarbonyl)piperidin-4-yl]methoxy]naphthalen-3-yl ester***

To 277 mg (0.881 mmol) of 2-chlorobenzenesulfonic acid 1-hydroxynaphthalen-3-yl ester, as prepared in the preceding step, 180 mg (0.837 mmol) of N-*tert*-butoxycarbonyl-4-piperidinemethanol, as prepared in step (b) of Example 1, 260 mg ((0.99 mmol) of triphenylphosphine, and 270 μL (2.45 mmol) of N-methylmorpholine in 2 mL of tetrahydrofuran, was added 160 μL (1.02 mmol) of diethyl azodicarboxylate. The reaction mixture was stirred at ambient temperature for 1 h. The reaction mixture was quenched with water, extracted into diethyl ether, dried ($MgSO_4$), and flash chromatographed (2% diethyl ether/methylene chloride) to give 325 mg (79% yield) of a colorless foam. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.17 (d, 1 H, J = 7 Hz), 7.96 (dd, 1 H, J = 1.4, 8 Hz), 7.41 - 7.67 (m, 5 H), 7.34 (dt, 1 H, J = 1, 7 Hz), 7.08 (d, 1 H), 6.64 (d, 1 H), J = 2 Hz), 4.18 (br, 2 H), 3.89 (d, 2 H, J = 6.2 Hz), 2.79 (t, 2 H, J = 12 H), 2.0 - 2.2 (m, 1 H), 1.76 (d, 2 H, J = 8 Hz), and 1.49 (s, 9 H). Mass spectrum (MALDI-TOF; α-cyano-4-hydroxycinnamic acid matrix) calcd. for $C_{27}H_{30}ClNO_6S$: 554.1 (M + Na). Found: 554.2.

c) ***2-Chlorobenzenesulfonic acid 1-[(piperidin-4-yl)methoxy]naphthalen-3-yl ester hydrochloride***

To a solution of 319 mg (0.596 mmol) of 2-chlorobenzenesulfonic acid 1-[[1-N-(*tert*-butoxycarbonyl)piperidin-4-yl]methoxy]naphthalen-3-yl ester, as prepared in the preceding step, in 2 mL of methylene chloride was added 1.5 mL (6 mmol) of 4 N HCl in dioxane. The reaction mixture was stirred for 1 h and triturated with diethyl ether to afford 281 mg of the title compound as a colorless powder. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.94 (bd, 1 H, J = 9 Hz), 8.68 (bd, 1 H, J = 10 Hz), 8.6 (d, 1 H, J = 8 Hz), 7.8 - 7.98 (m, 4 Hz), 7.50 - 7.6 (m, 3 H), 7.18 (d, 1 H, J = 2 Hz), 6.69 (d, 1 H, J = 2 H), 3.94 (d, 2 H, J = 7 Hz), 2.93 (q, 2 H), 2.16 (bm, 1 H), 1.96 (d, 2 H), and 1.57 - 1.71 (m, 2 H). Mass spectrum (MALDI-TOF; gentisic acid matrix) calcd. for $C_{22}H_{22}ClNO_4S$: 432.1 (M + H). Found: 431.5.

d) *2-Chlorobenzenesulfonic acid 1-[[(1-acetimidoyl)piperidin-4-yl]methoxy]naphthalen-3-yl ester acetic acid salt*

A mixture of 100 mg (0.214 mmol) of 2-chlorobenzenesulfonic acid 1-[(piperidin-4-yl)methoxy]naphthalen-3-yl ester hydrochloride, as prepared in the preceding step, in N,N-dimethylformamide (2 mL) containing 55 mg (0.45 mmol) of ethyl acetimidate hydrochloride and 125 μL of N,N-diisopropylethylamine was stirred at ambient temperature overnight. To the reaction mixture was added another 125 μL of N,N-diisopropylethylamine and 55 mg (0.45 mmol) of ethyl acetimidate hydrochloride. The reaction mixture was stirred for another 4 h. The reaction mixture was concentrated to dryness, quenched with 1 N sodium hydroxide (2 mL), extracted into methylene chloride, dried (K_2CO), and concentrated *in vacuo*. The residue was diluted with methylene chloride (1 mL), treated with 1 mL of glacial acetic acid and directly purified by preparative thin layer chromatography using methylene chloride/methanol/glacial acetic acid (93.6:6.5:0.5) as developing solvent to give the title compound. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.14 (d, 1 H, J = 8 Hz), 7.8 - 7.97 (m, 4 H), 7.50 - 7.59 (m, 3 H), 7.19 (s, 1 H), 6.68 (d, 1 H, J = 2 Hz), 4.11 (d, 2 H, J = 6 Hz), 3.92 (d, 2 H, J = 6 Hz), 3.11 (t, 2 H, J = 2.6 Hz), 2.2 (m, 1 H), 1.92 (d, 2 H), 1.75 (br s, 3 H), and 1.41 (q, 2 H). Mass spectrum (MALDI-TOF; α-cyano-4-hydroxycinnamic acid matrix) calcd. for $C_{23}H_{24}ClN_3O_4S$: 474.1 (M + H). Found: 473.8.

Example 13

3-[(2-Chlorophenoxy)methyl]-[[(1-acetimidoyl)piperidin-4-yl]methoxy]benzene acetic acid Salt

a) 3-[(2-Chlorophenoxy)methyl]phenol

At 0°C to 616 mg (2.35 mmol) of triphenylphosphine and 400 μL (3.84 mmol) of 2-chlorophenol in 20 mL of methylene chloride was added 370 mL (2.35 mmol) of diethyl azodicarboxylate followed by dropwise addition of a solution of 233 mg (1.9 mmol) 3-hydroxybenzyl alcohol in 2 mL of tetrahydrofuran. The reaction mixture was stirred at 0°C to ambient temperature for 1 h. The reaction mixture was quenched with water, extracted into diethyl ether, dried ($MgSO_4$), and purified by flash chromatography (methylene chloride/hexane (2:1 to 4:1)) to provided 227 mg (44% yield) of the title compound as a colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.39 (dd, 1 H, J = 1.6, 7.8 Hz), 7.25 (t, 1 H), 7.15 - 7.21 (m, 1 H), 6.88 -7.01 (m, 4 H), 6.79 (dd, 1 H, J = 2.5, 8.1 Hz), 5.12 (s, 2 H), and 4.97 (s, 1 H).

b) 1-[(2-Chlorophenoxy)methyl]-3-[[N-(*tert*-butoxycarbonyl)piperidin-4-yl]methoxy]benzene

To a solution of 272 mg (0.809 mmol) of 3-[(2-chlorophenoxy) methyl]phenol, as prepared in the preceding step, in methylene chloride (5 mL) containing 275 mg (1.05 mmol) of triphenylphosphine and 208 mg (0.97 mmol) of N-(*tert*-butoxycarbonyl)-4-piperidinemethanol, as prepared in step (b) of Example 1, was added slowly 165 μL (1.04 mmol) of diethyl azodicarboxylate. The reaction mixture was stirred at ambient temperature for 1 h. The reaction mixture was quenched with water, extracted into diethyl ether, dried ($MgSO_4$), and flash chromatographed (hexane/ethyl acetate (1:4 to 1:2)) to give 221 mg (58% yield) of the title compound as a colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.38 (dd, 1 H, J = 1.5, 7.8 Hz), 7.28 (t, 1 H, J = 8.1 Hz), 7.15 - 7.21 (m, 1 H), 8.82 - 7.03 (m, 5 H), 5.13 (s, 2 H), 3.82 (d, 2 H, J = 6.4 Hz), 2.74 (t, 2 H), 1.91 - 2.00 (m, 1 H), 1.84 (d, 2 H), and 1.47 (s, 9 H). Mass spectrum (MALDI-TOF;

α-cyano-4-hydroxycinnamic acid matrix) calcd. for $C_{24}H_{30}ClNO_4S$: 454.2 (M + Na). Found: 454.4.

c) 1-[(2-Chlorophenoxy)methyl]-3-[(piperidin-4-yl)methoxy]benzene hydrochloride

A solution of 215 mg of 1-[(2-chlorophenoxy)methyl]-3-[[N-(*tert*-butoxycarbonyl)piperidin-4-yl]methoxy]benzene, as prepared in the preceding step, in methylene chloride (2 mL) was treated with 1.5 mL of 4 N HCl in dioxane. The reaction mixture was stirred at ambient temperature for 1 h, and then concentrated to provide 183 mg of the title compound as a colorless powder after repeated concentrations from diethyl ether/hexane/methanol. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 8.51 (br s, 2 H), 7.45 (dd, 1 H, J = 1.3, 7.9 Hz), 7.27 - 7.35 (m, 2 H), 7.21 (d, 1 H), 6.90 - 7.05 (m, 4 H), 5.18 (s, 2 H), 3.87 (d, 2 H), 2.90 (t, 2 H, J = 10 Hz), 2.05 (m, 1 H), 1.91 (d, 2 H, J = 13.8 Hz), and 1.5 - 1.54 (m, 2 H). Mass spectrum (MALDI-TOF; α-cyano-4-hydroxycinnamic acid matrix) calcd. for $C_{19}H_{22}ClNO_2$: 332.1 (M + H). Found: 332.0.

d) 3-[(2-Chlorophenoxy)methyl]-[[(1-acetimidoyl)piperidin-4-yl]methoxy] benzene acetic acid salt

To 40 mg (0.109 mmol) of 1-[(2-chlorophenoxy)methyl]-3-[(piperidin-4-yl)methoxy]benzene hydrochloride as prepared in the preceding step, in 1 mL of N,N-dimethylformamide containing 100 μL (0.908 mmol) of N,N-diisopropylethylamine was added 40 mg (0.325 mmol) of ethyl acetimidate hydrochloride. The reaction mixture was stirred at ambient temperature for 3 days. The reaction mixture was concentrated *in vacuo* and the residue was quenched with 1 N sodium hydroxide, extracted into methylene choride, dried (K_2CO_3), and concentrated. The residue was dissolved with 1 mL of methylene chloride and then treated with 500 μL of glacial acetic acid. The solution was then applied directly to preparative thin layer chromatography using methylene chloride/methanol/glacial acetic (83:15:2) as developing solvent to provide 33.8 mg of the title compound as a gum. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 7.45 (dd,

1 H, J = 1.5, 7.9 Hz), 7.27 - 7.34 (m, 2 H), 7.20 - 7.23 (dd, 1 H, J = 1.4, 8.3 Hz), 6.89 - 7.04 (m, 4 H), 5.76 (s, 2 H), 4.07 (d, 2 H, J = 14 Hz), 3.87 (d, 2 H, J = 6.2 Hz), 3.05 (t, 2 H, J = 13 Hz), 2.22 (s, 3 H), 2.05 -2.13 (m, 1 H), 1.85 (d, 2 H), 1.71 (br s , 3 H), and 1.18 - 1.38 (m, 2 H). Mass spectrum (MALDI-TOF; α-cyano-4-hydroxycinnamic acid matrix matrix) calcd. for $C_{21}H_{25}N_2O_2$: 373.2 (M + H). Found: 373.0.

Example 14

2-Chlorobenzenesulfonic acid 3-[3-amidinopropoxy]-5-methylphenyl ester hydrochloride

a) 2-Chlorobenzenesulfonic acid 3-[3-cyanopropoxy]-5-methylphenyl ester

At 0°C to 250 mg (0.796 mmol) of 2-chlorobenzenesulfonic acid 3-hydroxy-5-methylphenyl ester, as prepared in step (c) of Example 1 in N,N-dimethylformamide (3 mL) was added 20 mg (0.833 mmol) of 100% sodium hydride. The reaction mixture was stirred for 5 min. To the reaction mixture was added 100 μL (1.01 mmol) of 4-bromobutyronitrile. The reaction mixture was stirred to ambient temperature overnight, quenched with 1 N hydrochloric acid and extracted into diethyl ether. The reaction mixture was dried ($MgSO_4$), placed on a silica gel flash column, and eluted with methylene chloride to give 127 mg of impure compound as an oil, which was used as is in the next reaction. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 7.94 (dd, 1 H, J = 1.5, 9 Hz), 7.54 - 7.63 (m, 2 H), 7.34 - 7.40 (m, 1 H), 6.57 (m, 1 H), 6.55 (m, 1 H), and 6.48 (t, 1 H, J = 2 Hz). Mass spectrum (MALDI-TOF; α-cyano-4-hydroxycinnamic acid matrix) calcd. for $C_{17}H_{16}ClNO_4S$: 388.0 (M + Na). Found: 387.8.

b) 2-Chlorobenzenesulfonic acid 3-[3-amidinopropoxy]-5-methylphenyl ester hydrochloride

A solution of 115 mg of 2-chlorobenzenesulfonic acid 3-[3-cyanopropoxy]-5-methylphenyl ester in 10 mL of 37% HCl in ethanol was stirred at 0°C overnight. The reaction was concentrated to dryness, diluted with ethanol

(5 mL) and treated with 1 g of ammonium carbonate. The reaction mixture was stirred for 40 min. The reaction mixture was quenched with 2 N sodium hydroxide, extracted into methylene chloride, dried (K_2CO_3), and concentrated to dryness. The residue was triturated with a mixture of methylene chloride/methanol/hexane to give 64 mg of the title compound as a colorless powder. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.02 (br s, 2 H), 8.68 (br s, 2 H), 7.95 (dd, 1 H, J = 1, 7 Hz), 7.81 - 7.90 (m, 2 H), 7.56 - 7.62 (m, 1 H), 6.75 (s, 1 H), 6.50 (s, 1 H), 6.44 (t, 1 H, J = 1 Hz), 3.89 (t, 2 H, J = 6 Hz), 2.21 (s, 2 H), and 2.02 (pentet, 2 H). Mass Spectrum (MALDI-TOF; α-cyano-4-hydroxycinnamic acid matrix) calcd. for $C_{17}H_{19}ClN_2O_4S$: 383.1 (M + H). Found: 382.8.

Example 15

2-Chlorobenzenesulfonic acid 3-[[3-(N-methylamidino)phenyl]methoxy]-5-methylphenyl ester hydrochloride

To a solution of 2-chlorobenzenesulfonic acid 3-[(3-cyanophenyl)methoxy]-5-methylphenyl ester (414 mg, 1.0 mmol), as prepared in step (a) of Example 6, in methylene chloride (10 mL) was added 37 % HCl in ethanol (15 mL) at 0°C. The mixture was allowed to stand at 0°C for 3 days. The solvent was evaporated and the residue was concentrated *in vacuo* from methylene chloride several times. The residue was dissolved in ethanol (10 mL), treated with methylamine hydrochloride (270 mg, 4.0 mmol) and Na_2CO_3 (212 mg, 2.0 mmol), and then stirred at room temperature for 2 days. The reaction mixture was partitioned between methylene chloride (150 mL) and 10% K_2CO_3. The organic phase was washed with 10% K_2CO_3 (50 mL) and dried over K_2CO_3. After removing the solvent *in vacuo*, HCl in methanol (30 mL) was added and the solvent was removed *in vacuo*. The residue was then purified by flash column chromatography (10% methanol/methylene chloride) and crystallized from methanol/ethyl acetate to give the title compound as white crystals (145 mg,

30%). ^{1}H-NMR (300 MHz, DMSO-d_6) δ 2.22 (s, 3 H), 3.01 (s, 3 H), 5.10 (s, 2 H), 6.53 (s, 1 H), 6.56 (s, 1 H), 6.87 (s, 1 H), 7.58 (t, 1 H, J = 7.0 Hz), 7.63 (t, 1 H, J = 7.6 Hz), 7.73 (m, 2 H), 7.86 (m, 3 H), 7.94 (d, 1 H, J = 4.0 Hz), 9.05 (br s, 1 H), 9.55 (br s, 1 H), and 9.94 (br s, 1 H). Mass spectrum (MALDI-TOF, sinapinic acid matrix) calcd. for $C_{22}H_{21}N_2O_4SCl$: 445.1 (M+ H). Found: 445.0.

Example 16

2-Chlorobenzenesulfonic acid 3-[(4-amidinophenyl)methoxy]-5-methylphenyl ester hydrochloride

a) 2-Chlorobenzenesulfonic acid 3-[(4-cyanophenyl)methoxy]-5-methylphenyl ester

Diethyl azodicarboxylate (524 mg, 3.0 mmol) was added to a solution of 2-chlorobenzenesulfonic acid 3-hydroxy-5-methylphenyl ester (900 mg, 3.0 mmol), as prepared in step (c) of the Example 1, 4-cyanobenzyl alcohol (400 mg, 3.0 mmol; Yoon *et al., J. Org. Chem. 38*:2786-2792 (1973)), and triphenylphosphine (790 mg, 3.0 mmol) in tetrahydrofuran (20 mL) at 0 °C. The mixture was stirred at 0 °C for 2 h and at room temperature for 3 h. The reaction mixture was quenched with water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The organic phase was washed sequentially with saturated $NaHCO_3$ (2 x 50 mL) and brine (2 x 50 mL), and dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (2:1 ethyl acetate:hexane) to give the title compound as a white solid (0.95 g, 76 %). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.26 (s, 3H), 5.03 (s, 2H), 6.57 (t, 1H, J = 2.2 Hz), 6.59 (s, 1H), 6.67 (s, 1H), 7.38 (t, 1H, J = 5.8 Hz), 7.49 (d, 2H, J = 4.2 Hz), 7.60 (m, 2H), 7.67 (d, 2H, J = 3.5 Hz) and 7.96 (d, 1H, J = 3.6 Hz).

b) 2-Chlorobenzenesulfonic acid 3-[(4-amidinophenyl)methoxy]-5-methylphenyl ester hydrochloride

To a solution of 2-chlorobenzenesulfonic acid 3-[(4-cyanophenyl)methoxy]-5-methylphenyl ester (414 mg, 1.0 mmol), as prepared in the preceding step, in methylene chloride (10 mL) was added 37% HCl in ethanol (20 mL) at 0 °C. The mixture was stirred at room temperature for 2 days. The solvent was evaporated and the residue was co-evaporated with methylene chloride several times. The residue was then dissolved in ethanol (20 mL) and ammonium carbonate (385 mg, 4.0 mmol) was added at 0 °C. The mixture was stirred at room temperature overnight. The reaction mixture was partitioned between methylene chloride and 10% K_2CO_3 (50 mL). The organic phase was washed with 50 mL of 10% K_2CO_3 and dried over K_2CO_3. The solvent was removed *in vacuo*. The residue was diluted with CH_2Cl_2, treated with HCl in methanol (30 mL), and concentrated. The residue was then purified by crystallization (methanol and ethyl acetate) to give the title compound as a white solid (345 mg, 74 %). ^{1}H-NMR (300 MHz, DMSO-d_6) δ 2.21 (s, 3H), 5.16 (s, 2H), 6.53 (t, 2 H, J = 9.3 Hz)), 6.86 (s, 1H), 7.55-7.62 (m, 3H), 7.82-7.89 (m, 4 H), 7.93 (d, 1H, J = 4.0 Hz), 9.24 (br s, 2 H) and 9.44 (br s, 2 H). Mass spectrum (MALDI-TOF, sinapinic acid matrix) calcd. for $C_{21}H_{19}N_2ClO_4S$: 431.1 (M+ H). Found: 431.1.

Example 17

2-Chlorobenzenesulfonic acid 3-[(3-amidinophenyl)methoxy]phenyl ester hydrochloride

a) 3-Benzyloxyphenyl acetate

Resorcinol monoacetate (6.10 g, 40 mmol) in DMF (10 mL) was added dropwise to the mixture of NaH (95%, 0.92 g, 40 mmol) in DMF (50 mL). The mixture was stirred at room temperature for 10 min. Benzyl bromide (6.85 g, 40 mmol) in DMF (10 mL) was then added dropwise, and the mixture was stirred at room temperature for 2 h. The reaction mixture was quenched slowly with water (100 mL) and then extracted with ethyl acetate (3 x 100 mL). The organic phase was washed with brine (2 x 50 mL) and dried over Na_2SO_4. The solvent was

removed *in vacuo* and the residue purified by flash column chromatography (1:1 hexane:methylene chloride) to give the title compound as a white solid (5.30 g, 55%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.28 (s, 3 H), 5.03 (s, 2 H), 6.72 (m, 2 H), 6.85 (dd, 1 H, J = 1.2, 4.1 Hz), 7.27 (t, 1 H, J = 7.9 Hz), and 7.41 (m, 5 H).

b) 3-Benzyloxyphenol

3-Benzyloxyphenyl acetate (4.84 g, 20 mmol), as prepared in the preceding step, in tetrahydrofuran (50 mL) was treated with 1 N NaOH (30 mL) at room temperature for 3 h. The mixture was acidified with 1 N HCl and extracted with ethyl acetate (3 x 100 mL). The organic phase was washed with brine (2 x 50 mL) and dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue purified by flash column chromatography (methylene chloride) to give the title compound as a colorless liquid (3.80 g, 96%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.01 (s, 2 H), 5.09 (s, 1 H), 6.47 (t, 2 H, J = 2.2 Hz), 6.56 (dd, 1 H, J = 1.1, 4.1 Hz), 7.11 (t, 1 H), and 7.39 (m, 5 H).

c) 2-Chlorobenzenesulfonic acid 3-benzyloxyphenyl ester

3-Benzyloxyphenol (2.97 g, 15 mmol), as prepared in the preceding step, in methylene chloride (50 mL) was treated with diisopropylethylamine (2 mL) and 2-chlorobenzenesulfonyl chloride (3.27 g, 15.5 mmol) at 0 °C for 2 h and at room temperature for 2 h. The reaction mixture was diluted with 200 mL of methylene chloride, washed sequentially with saturated $NaHCO_3$ (2 x 50 mL) and brine (2 x 50 mL), and dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (1:1 hexane:methylene chloride) to give the title compound as a colorless liquid (5.35 g, 95%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.97 (s, 2 H), 6.71 (dd, 1H, J = 1.1, 4.1 Hz), 6.78 (t, 1 H, J = 2.3 Hz), 6.85 (dd, 1 H, J = 1.1, 4.1 Hz), 7.17 (t, 1H, J = 8.3 Hz), 7.37 (m, 5 H), 7.58 (m, 2 H), and 7.91 (dd, 1 H, J = 1.1, 4.1 Hz).

d) ***2-Chlorobenzenesulfonic acid 3-hydroxyphenyl ester***

2-Chlorobenzenesulfonic acid 3-benzyloxyphenyl ester (3.75 g, 10 mmol), as prepared in the preceding step, Pd/C (10%) (350 mg) in tetrahydrofuran (80 mL) was hydrogenated (balloon) for 3 h. The catalyst was filtered through Celite and washed with tetrahydrofuran. The combined tetrahydrofuran solution was evaporated *in vacuo* and the residue was then purified by flash column chromatography (methylene chloride) to give the title compound as a colorless oil (2.75 g, 95%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.68 (m, 3 H), 7.12 (t, 1H, J = 6.5 Hz), 7.37 (t, 1H, J = 7.1 Hz), 7.60 (m, 2 H), 7.94 (dd, 1H, J = 0.6, 4.0 Hz).

e) ***2-Chlorobenzenesulfonic acid 3-[(3-cyanophenyl)methoxy]phenyl ester***

Diethyl azodicarboxylate (174 mg, 1.0 mmol) was added to a solution of 2-chlorobenzenesulfonic acid 3-hydroxyphenyl ester (285 mg, 1.0 mmol), as prepared in the preceding step, 3-cyanobenzyl alcohol (133 mg, 1.0 mmol)(Yoon *et al., J. Org. Chem. 38*:2786-2792 (1973)), and triphenylphosphine (263 mg, 1.0 mmol) in tetrahydrofuran (10 mL) at 0 °C. The mixture was stirred at 0 °C for 2 hours and at room temperature for 3 hours. The reaction mixture was quenched with water (30 mL) and extracted with ethyl acetate (3 x 30 mL). The organic phase was washed with saturated $NaHCO_3$ (2 x 30 mL), brine (2 x 30 mL) and dried over Na_2SO_4. The solvent was removed *in vacuo* the residue was purified by flash column chromatography (2:1 ethyl acetate:hexane) to give the title compound as a pale yellow oil (375 mg, 93 %). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.02 (s, 2 H), 6.78 (m, 2H), 6.85 (dd, 1H, J = 4.2, 1.3 Hz), 7.20 (t, 1H, J = 8.2 Hz), 7.38 (t, 1H, J = 5.8 Hz), 7.51 (t, 1H, J = 7.7 Hz), 7.59-7.68 (m, 5 H) and 7.93 (dd, 1 H, J = 4.0, 0.7 Hz).

f) ***2-Chlorobenzenesulfonic acid 3-[(3-amidinophenyl)methoxy]phenyl ester hydrochloride***

To a solution of 2-chlorobenzenesulfonic acid 3-[(3-cyanophenyl)methoxy]phenyl ester (280 mg, 0.7 mmol), as prepared in the preceding step, in methylene chloride (10 mL) was added 37 % HCl in ethanol (15

mL) at 0°C. The mixture was stirred at room temperature for 2 days. The solvent was evaporated and the residue was co-evaporated with methylene chloride several times. The residue was then dissolved in ethanol (10 mL) and ammonium carbonate (300 mg, 3.0 mmol) was added at 0°C. The mixture was stirred at room temperature overnight. The reaction mixture was diluted with methylene chloride (150 mL), washed with 10% K_2CO_3 (2 x 50 mL), and dried over K_2CO_3. The solvent was removed *in vacuo*, HCl in methanol (30 mL) was added, and then concentrated *in vacuo*. The residue was purified by flash chromatography (10 % methanol in methylene chloride) to give the title compound as a white foam (238 mg, 75%). ^{1}H-NMR (300 MHz, DMSO-d6) δ 5.15 (s, 2 H), 6.67 (d, 1 H, J = 4.0 Hz), 6.81 (s, 1 H), 7.03 (d, 1H, J = 4.0 Hz), 7.32 (t, 1 H, J = 8.3 Hz), 7.58 (t, 1 H, J = 7.5 Hz), 7.65 (t, 1 H, J = 7.7 Hz), 7.75-7.94 (m, 6 H), 9.27 (br s, 2 H), and 9.45 (br s, 2 H). Mass spectrum (MALDI-TOF, sinapinic acid matrix) calcd. for $C_{20}H_{17}N_2ClO_4S$: 417.1 (M + H), 439.0 (M + Na). Found: 417.4, 439.1.

Example 18

2-Chlorobenzenesulfonic acid 3-[5-amidinopentyloxy]-5-methylphenyl ester acetic acid salt

a) 2-Chlorobenzenesulfonic acid 3-[5-cyanopentyloxy]-5-methylphenyl ester

Sodium hydride (24 mg, 1 mmol; 100%) was added to solution of 250 mg (0.855 mmol) of 2-chlorobenzenesulfonic acid 3-hydroxy-5-methylphenyl ester, as prepared in step (c) of Example 1, in 2 mL of N,N-dimethylformamide. After 5 min, 130 μL (0.93 mmol) of 6-bromohexanenitrile was added to the reaction mixture. The reaction mixture was stirred for 2 h at ambient temperature, quenched with brine (50 mL), extracted into diethyl ether (50 mL), washed with water (3 x 10 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by flash chromatography (methylene chloride/petroleum ether 4:1 to 100:0) to give 250 mg of the title compound as a colorless oil which solidified

upon standing. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.97 (dd, 1 H, J = 1.4, 7.8 Hz), 7.56 - 7.65 (m, 2 H), 7.36 - 7.41 (m, 1 H), 6.59 (br s, 1 H), 6.53 (br, s 1 H), 6.48 (t, 1 H, J = 1.1 Hz), 3.85 (t, 2 H), 2.38 (t, 2 H), 2.24 (s, 3 H), and 1.6 - 1.8 (m, 6 H). Mass spectrum (MALDI-TOF, α-cyano-4-hydroxycinnamic acid matrix) calcd. for $C_{19}H_{20}NClO_4S$: 416.1 (M + Na). Found: 416.1.

b) 2-Chlorobenzenesulfonic acid 3-[5-amidinopentyloxy]-5-methylphenyl ester acetic acid salt

A solution of 138 mg (0.351 mmol) of 2-chlorobenzenesulfonic acid 3-[5-cyanopentyloxy]-5-methylphenyl ester, as prepared in the preceding step, in 10 mL of 37% HCl ethanol was stirred at ambient temperature overnight. The reaction mixture was concentrated to an oil, diluted with 5 mL of ethanol and treated with 1.0 g of ammonium carbonate. After stirring at ambient temperature for 30 min, the reaction mixture was quenched with 2 N NaOH, extracted into methylene chloride, dried (K_2CO_3), and concentrated. The residue was treated with 500 μL of glacial acetic acid and triturated from diethyl ether/methylene chloride to provide 3.9 mg of the title compound. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 7.79 - 7.95 (m, 3 H), 7.55 - 7.60 (t, 1 H), 6.73 (s, 1 H), 6.49 (s, 1 H), 6.38 (s, 1H), 3.85 (t, 2 H), 2.29 (t, 2 H), and 2.20 (s, 3 H). Mass spectrum (MALDI-TOF, α-cyano-4-hydroxycinnamic acid matrix) calcd. for $C_{19}H_{23}N_2ClO_4S$: 411.1 (M + H). Found: 411.3.

Example 19

In Vitro Inhibition of Purified Enzymes

Reagents

All buffer salts were obtained from Sigma Chemical Company (St. Louis, MO), and were of the highest purity available. The enzyme substrates, N-benzoyl-Phe-Val-Arg-*p*-nitroanilide (Sigma B7632), N-benzoyl-Ile-Glu-Gly-Arg-*p*-nitroanilide (Sigma B2291), N-*p*-tosyl-Gly-Pro-Lys-*p*-nitroanilide (Sigma

T6140), and N-succinyl-Ala-Ala-Pro-Phe-*p*-nitroanilide (Sigma S7388) were all obtained from Sigma.

Human α-thrombin and human factor Xa were obtained from Enzyme Research Laboratories (South Bend, Indiana). Bovine trypsin was obtained from Sigma.

***K_i* Determinations**

All assays are based on the ability of the test compound to inhibit the enzyme catalyzed hydrolysis of a peptide *p*-nitroanilide substrate. In a typical K_i determination, substrate is prepared in DMSO, and diluted into an assay buffer consisting of 50mM HEPES, 200 mM NaCl, pH 7.5. The final concentration for each of the substrates is listed below. In general, substrate concentrations are lower than the experimentally determined value for K_m. Test compounds are prepared as a 0.16 mg/mL solution in DMSO. Dilutions are prepared in DMSO yielding 8 final concentrations encompassing a 200-fold concentration range. Enzyme solutions are prepared at the concentrations listed below in assay buffer.

In a typical K_i determination, into each well of a 96 well plate is pipetted 280 uL of substrate solution, 10 μL of inhibitor solution, and the plate allowed to thermally equilibrate at 37°C in a Molecular Devices plate reader for >10 minutes. Reactions were initiated by the addition of a 20 μL aliquot of enzyme, and the absorbance increase at 405 nm is recorded for 15 minutes. Data corresponding to less than 10% of the total substrate hydrolysis were used in the calculations. The ratio of the velocity (rate of the change in absorbance as a function of time) for a sample containing no inhibitor is divided by the velocity of a sample containing inhibitor, and is plotted as a function of inhibitor concentration. The data are fit to a linear regression, and the value of the slope of the line calculated. The inverse of the slope is the experimentally determined K_i value.

Thrombin

Thrombin activity was assessed as the ability to hydrolyze the substrate Suc-Ala-Ala-Pro-Arg-*p*NA. Substrate solutions were prepared at a concentration of 20 μM (20uM<<K_m=180 μM) in assay buffer. Final DMSO concentration was 0.3%. Purified human α-thrombin was diluted into assay buffer to a concentration of 450 nM. Final reagent concentrations were: [thrombin] = 0.5 nM, [Suc-Ala-Ala-Pro-Arg-*p*NA] = 20 μM.

Factor Xa

Factor Xa activity was assessed as the ability to hydrolyze the substrate Bz-Ile-Glu-Gly-Arg-*p*NA. Substrate solutions were prepared at a concentration of 51 μM (51 μM<<K_m=1.3 mM) in assay buffer. Final DMSO concentration was 0.3%. Purified activated human Factor Xa was diluted into assay buffer to a concentration of 300 nM. Final reagent concentrations were: [FXa] = 20 nM, [Bz-Ile-Glu-Gly-Arg-*p*NA] = 51 μM.

Trypsin

Trypsin activity was assessed as the ability to hydrolyze the substrate Bz-Phe-Val-Arg-*p*NA. Substrate solutions were prepared at a concentration of 14 μM (14 μM<<K_m=291 μM) in assay buffer. Final DMSO concentration was 0.3%. Purified bovine trypsin was diluted into assay buffer to a concentration of 150 nM. Final reagent concentrations were: [Trypsin] = 10 nM, [Bz-Phe-Val-Arg-*p*NA] = 14 μM.

Chymotrypsin

Chymotrypsin activity was assessed as the ability to hydrolyze the substrate Suc-Ala-Ala-Pro-Phe-*p*NA. Substrate solutions were prepared at a concentration of 14 μM (14 μM<<K_m= 61uM) in assay buffer. Final DMSO concentration was 0.3%. Purified bovine α-chymotrypsin was diluted into assay

buffer to a concentration of 45 nM. Final reagent concentrations were: [chymotrypsin] = 3 nM, [Suc-Ala-Ala-Pro-Phe-*p*NA] = 14 μM.

The results obtained employing synthesized compounds are given in Table 1.

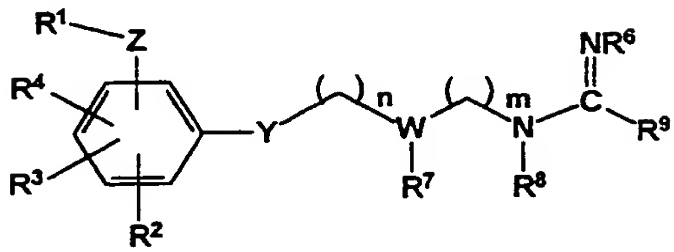
Product of Example Number	Enzyme	K_i (μM)
1	Thrombin	1.65
5	Thrombin	4.86
6	Factor Xa	2.72
7	Trypsin	5.23
8	Thrombin	1.72
14	Thrombin	0.57
18	Chymotrypsin	6.29

The results indicate that the compounds of the present invention are inhibitors of proteases. Compounds of the present invention inhibit a number of proteases, including factor Xa, thrombin chymotrypsin and trypsin.

Having now fully described this invention, it will be understood to those of ordinary skill in the art that the same can be performed within a wide and equivalent range of conditions, formulations, and other parameters without affecting the scope of the invention or any embodiment thereof. All patents and publications cited herein are fully incorporated by reference herein in their entirety.

What Is Claimed Is:

1. A compound having the Formula *I*:



I

or solvates, hydrates or pharmaceutically acceptable salts thereof;

wherein:

Z is one of $-NR^{10}SO_2-$, $-SO_2NR^{10}-$, $-NR^{10}C(R^yR^z)-$, $-C(R^yR^z)NR^{10}-$, $-OSO_2-$, $-SO_2O-$, $-OC(R^yR^z)-$, $-C(R^yR^z)O-$, $-NR^{10}CO-$ or $-CONR^{10}-$;

R^y and R^z are each independently one of hydrogen, alkyl, cycloalkyl, aryl, aralkyl, hydroxyalkyl, carboxyalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl or carboxy;

R^1 is one of alkyl, cycloalkyl, alkenyl, alkynyl, aryl, aralkyl or heteroaryl, any of which may be optionally substituted;

R^2, R^3 and R^4 are each independently one of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, aralkyl, heteroaryl, trifluoromethyl, halogen, hydroxyalkyl, cyano, nitro, carboxamide, $-CO_2R^x$, $-CH_2OR^x$ or $-OR^x$, or when present on adjacent carbon atoms, R^2 and R^3 may also be taken together to form one of $-CH=CH-CH=CH-$ or $-(CH_2)_q-$, where q is from 2 to 6, and R^4 is defined as above;

R^x, in each instance, is independently one of hydrogen, alkyl or cycloalkyl wherein said alkyl or cycloalkyl groups may optionally have one or more unsaturations;

Y is one of $-O-$, $-NR^{10}-$, $-S-$, $-CHR^{10}-$ or a covalent bond;

W is N or CR^{10};

R^6, in each instance, is independently one of hydrogen, alkyl, hydroxy, alkoxy, aryloxy, aralkoxy, alkoxycarbonyloxy, cyano or $-CO_2R^w$, where R^w is alkyl or cycloalkyl;

R^7 and R^8 are each independently one of hydrogen, alkyl, aralkyl, aryl, hydroxyalkyl or carboxyalkyl, or R^7 and R^8 are taken together to form $-(CH_2)_y-$, where y is zero, 1 or 2, with the proviso that when W is N, y cannot be zero or 1;

R^9 is one of hydrogen, alkyl, cycloalkyl or aryl, wherein said alkyl, cycloalkyl or aryl can be optionally substituted with amino, monoalkylamino, dialkylamino, alkoxy, hydroxy, carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, aryl, heteroaryl, acylamino, cyano or trifluoromethyl;

R^{10}, in each instance, is independently one of hydrogen, alkyl, aralkyl, aryl, hydroxyalkyl, aminoalkyl, monoalkylamino(C_{2-10})alkyl, dialkylamino (C_{2-10})alkyl or carboxyalkyl;

n is from zero to 8, with the proviso that when W is N and Y is other than $-CHR^{10}-$, then n is from 2 to 8; and

m is from 1 to 4, provided that when W is N, then m is not 1.

2. A compound of claim 1, wherein:

Z is one of $-SO_2O-$, $-SO_2NR^{10}-$, $-C(R^yR^z)O-$ or $-OC(R^yR^z)-$, where R^y and R^z are each hydrogen;

R^1 is one of C_{6-10} aryl, pyridinyl, quinizolinyl, quinolinyl or tetrahydroquinolinyl, any of which is optionally substituted by one or two of hydroxy, nitro, trifluoromethyl, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} aminoalkyl, C_{1-6} aminoalkoxy, amino, mono(C_{1-4})alkylamino, di(C_{1-4})alkylamino, C_{2-6} alkoxycarbonylamino, C_{2-6} alkoxycarbonyl, carboxy, C_{1-6} hydroxyalkyl, C_{2-6} hydroxyalkoxy, C_{2-10} mono(carboxyalkyl)amino, di(C_{2-10} carboxyalkyl)amino, C_{6-14} ar(C_{1-6} alkoxycarbonyl, C_{2-6} alkynylcarbonyl, C_{1-6} alkylsulfonyl, C_{2-6} alkenylsulfonyl, C_{2-6} alkynylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonamido, amidino, guanidino, C_{1-6} alkyliminoamino, formyliminoamino, C_{2-6} carboxyalkyl,

C_{2-6} carboxyalkoxy, C_{2-6} carboxyalkylamino, cyano, trifluoromethoxy, or perfluoroethoxy;

R^2, R^3 and R^4 are independently one of hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, phenyl, benzyl, trifluoromethyl, halogen, hydroxy(C_{1-8})alkyl, cyano, nitro, carboxamide, carboxy, C_{1-4} alkoxycarbonyl, C_{1-4} alkoxymethyl or C_{1-4} alkoxy; or alternatively, R^2 and R^3, when present on adjacent carbon atoms, may also be taken together to form one of $-CH=CH-CH=CH-$ or $-(CH_2)_q-$, where q is from 2 to 6, and R^4 is as defined above;

Y is one of $-O-$, $-S-$, $-NR^{10}-$, or a covalent bond;

W is N or CR^{10};

R^6, in each instance, is one of hydrogen, C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy, phenoxy, C_{1-4} alkyloxycarbonyl or cyano;

R^7 and R^8 are independently one of hydrogen, C_{1-6} alkyl, C_{2-10} carboxyalkyl or C_{2-10} hydroxyalkyl, or R^7 and R^8 are taken together to form $-(CH_2)_y-$ where y is 0, 1 or 2, provided that when W is N, y cannot be 0 or 1;

R^9 is hydrogen; or C_{1-10} alkyl, optionally substituted with amino, mono(C_{1-4})alkylamino, C_{1-6} alkoxy, hydroxy, carboxy, phenyl, alkyloxycarbonyl, aralkoxycarbonyl, C_{1-6} acylamino, cyano or trifluoromethyl;

R^{10}, in each instance, is independently hydrogen, C_{1-6} alkyl, benzyl, phenyl, C_{2-10} hydroxyalkyl, C_{2-10} aminoalkyl, C_{1-4} monoalkylamino(C_{2-8})alkyl, C_{1-4} dialkylamino(C_{2-8})alkyl or C_{2-10} carboxyalkyl;

n is from zero to 8, with the proviso that when W is N, then n is from 2 to 8; and

m is from 1 to 4, provided that when W is N, then m is not 1.

3. A compound of claim 1, wherein:

Z is one of $-SO_2O-$, $-SO_2NR^{10}-$, $-CH_2O-$ or $-OCH_2-$;

R^1 is one of phenyl or naphthyl, optionally substituted by one or two of chloro or dimethylamino;

R^2 and R^3 are each hydrogen or R^2 and R^3 may also be taken together to form $-CH=CH-CH=CH-$;

R^4 is one of hydrogen, methyl, methoxy or trifluoromethyl;

Y is one of O or NR^{10};

W is N or CR^{10};

R^6, in each instance is hydrogen or hydroxy;

R^7 and R^8 are independently one of hydrogen, C_{1-6} alkyl, C_{2-10} hydroxyalkyl or C_{2-10} carboxyalkyl, or R^7 and R^8 are taken together to form $-(CH_2)_y-$, where y is zero, 1 or 2, with the proviso that when W is N, y cannot be zero or 1;

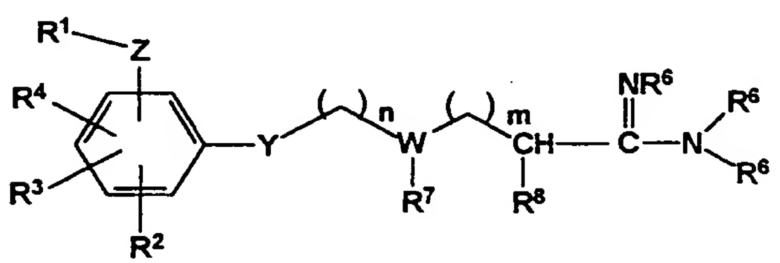
R^9 is hydrogen or C_{1-4} alkyl;

R^{10}, in each instance, is independently hydrogen, C_{1-4} alkyl, C_{2-4} hydroxyalkyl, C_{2-4} carboxyalkyl, C_{2-4} aminoalkyl, dimethylamino(C_{2-8})alkyl, methylamino(C_{2-8})alkyl;

n is from zero to 4, with the proviso that when W is N, then n is 2 to 4; and

m is 1, 2 or 3.

4. A compound having the Formula ***II***:



II

or solvates, hydrates or pharmaceutically acceptable salts thereof;

wherein:

Z is one of $-NR^{10}SO_2-$, $-SO_2NR^{10}-$, $-NR^{10}C(R^yR^z)-$, $-C(R^yR^z)NR^{10}-$, $-OSO_2-$, $-SO_2O-$, $-OC(R^yR^z)-$, $-C(R^yR^z)O-$, $-NR^{10}CO-$ or $-CONR^{10}-$;

R^y and R^z are each independently one of hydrogen, alkyl, cycloalkyl, aryl, aralkyl, hydroxyalkyl, carboxyalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl or carboxy;

R^1 is one of alkyl, cycloalkyl, alkenyl, alkynyl, aryl, aralkyl or heteroaryl, any of which may be optionally substituted;

R^2, R^3 and R^4 are each independently one of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, aralkyl, heteroaryl, trifluoromethyl, halogen, hydroxyalkyl, cyano, nitro, carboxamide, $-CO_2R^x$, $-CH_2OR^x$ or $-OR^x$, or when present on adjacent carbon atoms, R^2 and R^3 may also be taken together to form one of $-CH{=}CH-CH{=}CH-$ or $-(CH_2)_q-$, where q is from 2 to 6, and R^4 is defined as above;

R^x, in each instance, is independently one of hydrogen, alkyl or cycloalkyl wherein said alkyl or cycloalkyl groups may optionally have one or more unsaturations;

Y is one of $-O-$, $-NR^{10}-$, $-S-$, $-CHR^{10}-$ or a covalent bond;

W is N or CR^{10};

R^6, in each instance, is independently one of hydrogen, alkyl, hydroxy, alkoxy, aryloxy, aralkoxy, alkoxycarbonyloxy, cyano or $-CO_2R^w$, where R^w is alkyl or cycloalkyl;

R^7 and R^8 are each independently one of hydrogen, alkyl, aralkyl, aryl, hydroxyalkyl or carboxyalkyl, or R^7 and R^8 are taken together to form $-(CH_2)_y-$, where y is zero, 1 or 2, with the proviso that when W is N, y cannot be zero or 1;

R^{10}, in each instance, is independently one of hydrogen, alkyl, aralkyl, aryl, hydroxyalkyl, aminoalkyl, monoalkylamino(C_{2-10})alkyl, dialkylamino (C_{2-10})alkyl or carboxyalkyl;

n is from zero to 8, with the proviso that when W is N and Y is other than $-CHR^{10}-$, then n is from 2 to 8; and

m is from 1 to 4, provided that when W is N, then m is not 1.

5. A compound of claim 4, wherein:

Z is one of $-SO_2O-$, $-SO_2NR^{10}-$, $-C(R^yR^z)O-$ or $-OC(R^yR^z)-$, where R^y and R^z are each hydrogen;

R^1 is one of C_{6-10} aryl, pyridinyl, quinizolinyl, quinolinyl or tetrahydroquinolinyl, any of which is optionally substituted by one or two of hydroxy, nitro, trifluoromethyl, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} aminoalkyl, C_{1-6} aminoalkoxy, amino, mono(C_{1-4})alkylamino, di(C_{1-4})alkylamino, C_{2-6} alkoxycarbonylamino, C_{2-6} alkoxycarbonyl, carboxy, C_{1-6} hydroxyalkyl, C_{2-6} hydroxyalkoxy, C_{2-10} mono(carboxyalkyl)amino, di(C_{2-10} carboxyalkyl)amino, C_{6-14} ar(C_{1-6})alkoxycarbonyl, C_{2-6} alkynylcarbonyl, C_{1-6} alkylsulfonyl, C_{2-6} alkenylsulfonyl, C_{2-6} alkynylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonamido, amidino, guanidino, C_{1-6} alkyliminoamino, formyliminoamino, C_{2-6} carboxyalkoxy, C_{2-6} carboxyalkyl, C_{2-6} carboxyalkylamino, cyano, trifluoromethoxy, or perfluoroethoxy;

R^2, R^3 and R^4 are independently one of hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, phenyl, benzyl, trifluoromethyl, halogen, hydroxy(C_{1-8})alkyl, cyano, nitro, carboxamide, carboxy, C_{1-4} alkoxycarbonyl, C_{1-4} alkoxymethyl or C_{1-4} alkoxy; or alternatively, R^2 and R^3, when present on adjacent carbon atoms, may also be taken together to form one of $-CH=CH-CH=CH-$ or $-(CH_2)_q-$, where q is from 2 to 6, and R^4 is as defined above;

Y is one of $-O-$, $-S-$, $-NR^{10}-$ or a covalent bond;

W is N or CR^{10};

R^6, in each instance, is one of hydrogen, C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy, phenoxy, C_{1-4} alkyloxycarbonyl or cyano;

R^7 and R^8 are independently one of hydrogen, C_{1-6} alkyl, C_{2-10} carboxyalkyl or C_{2-10} hydroxyalkyl, or R^7 and R^8 are taken together to form $-(CH_2)_y-$ where y is 0, 1 or 2, provided that when W is N, y cannot be 0 or 1;

R^{10}, in each instance, is independently hydrogen, C_{1-6} alkyl, benzyl, phenyl, C_{2-10} hydroxyalkyl, C_{2-10} aminoalkyl, C_{1-4} monoalkylamino(C_{2-8})alkyl, C_{1-4} dialkylamino(C_{2-8})alkyl or C_{2-10} carboxyalkyl;

n is from zero to 8, with th proviso that when W is N, then n is from 2 to 8; and

m is from 1 to 4, provided that when W is N, then m is not 1.

6. A compound of claim 4, wherein:

Z is one of $-SO_2O-$, $-SO_2NR^{10}-$, $-CH_2O-$ or $-OCH_2-$;

R^1 is one of phenyl or naphthyl, optionally substituted by one or two of chloro or dimethylamino;

R^2 and R^3 are each hydrogen or R^2 and R^3 may also be taken together to form $-CH=CH-CH=CH-$;

R^4 is one of hydrogen, methyl, methoxy or trifluoromethyl;

Y is one of O or NR^{10};

W is N or CR^{10};

R^6, in each instance is hydrogen or hydroxy;

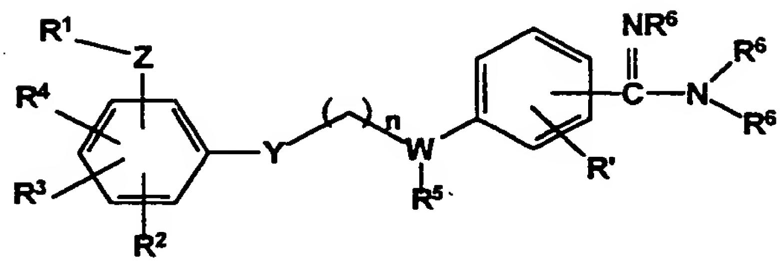
R^7 and R^8 are independently one of hydrogen, C_{1-6} alkyl, C_{2-10} hydroxyalkyl or C_{2-10} carboxyalkyl, or R^7 and R^8 are taken together to form $-(CH_2)_y-$, where y is zero, 1 or 2, with the proviso that when W is N, y cannot be zero or 1;

R^{10}, in each instance, is independently hydrogen, C_{1-4} alkyl, C_{2-4} hydroxyalkyl, C_{2-4} carboxyalkyl, C_{2-4} aminoalkyl, dimethylamino(C_{2-8})alkyl, methylamino(C_{2-8})alkyl;

n is from zero to 4, with the proviso that when W is N, then n is 2 to 4; and

m is 1, 2 or 3.

7. A compound having the Formula ***III***:



III

or solvates, hydrates or pharmaceutically acceptable salts thereof;

wherein:

Z is one of $-NR^{10}SO_2-$, $-SO_2NR^{10}-$, $-NR^{10}C(R^yR^z)-$, $-C(R^yR^z)NR^{10}-$, $-OSO_2-$, $-SO_2O-$, $-OC(R^yR^z)-$, $-C(R^yR^z)O-$, $-NR^{10}CO-$ or $-CONR^{10}-$;

R^y and R^z are each independently one of hydrogen, alkyl, cycloalkyl, aryl, aralkyl, hydroxyalkyl, carboxyalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl or carboxy;

R^1 is one of alkyl, cycloalkyl, alkenyl, alkynyl, aryl, aralkyl or heteroaryl, any of which may be optionally substituted;

R^2, R^3 and R^4 are each independently one of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, aralkyl, heteroaryl, trifluoromethyl, halogen, hydroxyalkyl, cyano, nitro, carboxamide, $-CO_2R^x$, $-CH_2OR^x$ or $-OR^x$, or when present on adjacent carbon atoms, R^2 and R^3 may also be taken together to form one of $-CH=CH-CH=CH-$ or $-(CH_2)_q-$, where q is from 2 to 6, and R^4 is defined as above;

R^x, in each instance, is independently one of hydrogen, alkyl or cycloalkyl wherein said alkyl or cycloalkyl groups may optionally have one or more unsaturations;

Y is one of $-O-$, $-NR^{10}-$, $-S-$, $-CHR^{10}-$ or a covalent bond;

W is N or CR^{10};

R^5 is one of hydrogen, alkyl, aralkyl, aryl, hydroxyalkyl or carboxyalkyl;

R^6, in each instance, is independently one of hydrogen, alkyl, hydroxy, alkoxy, aryloxy, aralk xy, alkoxycarbonyloxy, cyano or $-CO_2R^w$, where R^w is alkyl or cycloalkyl;

R^{10}, in each instance, is independently one of hydrogen, alkyl, aralkyl, aryl, hydroxyalkyl, aminoalkyl, monoalkylamino(C_{2-10})alkyl, dialkylamino(C_{2-10})alkyl or carboxyalkyl;

R' is one of hydrogen, alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, trifluoromethyl, halogen, hydroxyalkyl, cyano, nitro, carboxamide, carboxy, alkoxycarbonyl or alkoxyalkyl; and

n is from zero to 8, with the proviso that when W is N and Y is other than $-CHR^{10}-$, then n is from 2 to 8.

8. A compound of claim 7, wherein:

Z is one of $-SO_2O-$, $-SO_2NR^{10}-$, $-C(R^yR^z)O-$ or $-OC(R^yR^z)-$, where R^y and R^z are each hydrogen;

R^1 is one of C_{6-10} aryl, pyridinyl, quinizolinyl, quinolinyl or tetrahydroquinolinyl, any of which is optionally substituted by one or two of hydroxy, nitro, trifluoromethyl, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} aminoalkyl, C_{1-6} aminoalkoxy, amino, mono(C_{1-4})alkylamino, di(C_{1-4})alkylamino, C_{2-6} alkoxycarbonylamino, C_{2-6} alkoxycarbonyl, carboxy, C_{1-6} hydroxyalkyl, C_{2-6} hydroxyalkoxy, C_{2-10} mono(carboxyalkyl)amino, di(C_{2-10} carboxyalkyl)amino, C_{6-14} ar(C_{1-6} alkoxycarbonyl, C_{2-6} alkynylcarbonyl, C_{1-6} alkylsulfonyl, C_{2-6} alkenylsulfonyl, C_{2-6} alkynylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonamido, amidino, guanidino, C_{1-6} alkyliminoamino, formyliminoamino, C_{2-6} carboxyalkyl, C_{2-6} carboxyalkoxy, C_{2-6} carboxyalkylamino, cyano, trifluoromethoxy, or perfluoroethoxy;

R^2, R^3 and R^4 are independently one of hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, phenyl, benzyl, trifluoromethyl, halogen, hydroxy(C_{1-8})alkyl, cyano, nitro, carboxamide, carboxy, C_{1-4} alkoxycarbonyl, C_{1-4} alkoxymethyl or C_{1-4} alkoxy; or alternatively, R^2 and R^3, when present on adjacent carbon atoms, may

also be taken together to form one of –CH=CH–CH=CH– or –$(CH_2)_q$–, where q is from 2 to 6, and R^4 is as defined above;

Y is one of –O–, –S–, – NR^{10}– or a covalent bond;

W is N or CR^{10};

R^5 is one of hydrogen, C_{1-4} alkyl, C_{2-10} carboxyalkyl or C_{2-10} hydroxyalkyl;

R^6, in each instance, is one of hydrogen, C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy, phenoxy, C_{1-4} alkyloxycarbonyl or cyano;

R^{10}, in each instance, is independently hydrogen, C_{1-6} alkyl, benzyl, phenyl, C_{2-10} hydroxyalkyl, C_{2-10} aminoalkyl, C_{1-4} monoalkylamino(C_{2-8})alkyl, C_{1-4} dialkylamino(C_{2-8})alkyl or C_{2-10} carboxyalkyl;

R' is one of hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, phenyl, benzyl, trifluoromethyl, halogen, hydroxy(C_{1-8})alkyl, cyano, nitro, carboxamide, carboxy, alkoxycarbonyl, alkoxymethyl or alkoxy; and

n is from zero to 8, with the proviso that when W is N, then n is from 2 to 8.

9. A compound of claim 7, wherein:

Z is one of –SO_2O–, –SO_2NR^{10}–, –CH_2O– or –OCH_2–;

R^1 is one of phenyl or naphthyl, optionally substituted by one or two of chloro or dimethylamino;

R^2 and R^3 are each hydrogen or R^2 and R^3 may also be taken together to form –CH=CH–CH=CH–;

R^4 is one of hydrogen, methyl, methoxy or trifluoromethyl;

Y is one of O or NR^{10};

W is N or CR^{10};

R^5 is one of hydrogen, C_{1-6} alkyl, C_{2-10} hydroxyalkyl or C_{2-10} carboxyalkyl;

R^6, in each instance is hydrogen or hydroxy;

R^{10}, in each instance, is independently hydrogen, C_{1-4} alkyl, C_{2-4} hydroxyalkyl, C_{2-4} carboxyalkyl, C_{2-4} aminoalkyl, dimethylamino(C_{2-8})alkyl, methylamino(C_{2-8})alkyl;

R' is hydrogen, methyl, methoxy or trifluoromethyl; and

n is from zero to 4, with the proviso that when W is N, then n is 2 to 4.

10. The compound of claim 1, which is:

2-chlorobenzenesulfonic acid 3-[(1-acetimidoylpiperidin-4-yl)methoxy]-5-methylphenyl ester hydrochloride;

3-(2-chlorobenzyloxy)-5-methyl-1-[2-[(1-acetimidoyl)piperazin-4-yl]]ethoxybenzene diacetic acid salt;

N-[2-(N,N-dimethylamino)ethyl]-N-[2-[[4-(1-acetimidoyl)amino]butoxy]-4-methylphenyl]benzenesulfonamide dihydrochloride;

N-benzyl-N-[[[3-(1-acetimidoyl)piperidin-4-yl]methylamino]phenyl]-benzenesulfonamide;

3-chlorobenzenesulfonic acid 3-[[(1-acetimidoyl)piperidin-4-yl]methoxy]-5-methylphenyl ester hydrochloride;

2,3-dichlorobenzenesulfonic acid 3-[[(1-acetimidoyl)piperidin-4-yl]methoxy]-5-methylphenyl ester hydrochloride;

2-chloro-N-[[3-[(1-acetimidoyl)piperidin-4-yl]methoxy]-5-trifluoromethylphenyl]benzenesulfonamide hydrochloride;

2-chloro-N-(5-carboxypentyl)-N-[[3-[(1-acetimidoyl)piperidin-4-yl]methoxy]-5-trifluoromethylphenyl]benzenesulfonamide;

1-(5-(N,N-dimethylamino)naphthalenesulfonic acid 3-[[(1-acetimidoyl)piperidin-3-yl]methoxy]-5-methoxyphenyl ester hydrochloride;

2-chlorobenzenesulfonic acid 1-[[(1-acetimidoyl)piperidin-4-yl]methoxy]naphthalen-3-yl ester acetic acid salt; or

3-[(2-chlorophenoxy)methyl]-[[(1-acetimidoyl)piperidin-4-yl]methoxy]benzene acetic acid salt.

11. The compound of claim 4, which is:

2-chlorobenzenesulfonic acid 3-[3-amidinopropoxy]-5-methylphenyl ester hydrochloride; or

2-chlorobenzenesulfonic acid 3-[5-amidinopentyloxy]-5-methylphenyl ester acetic acid salt.

12. The compound of claim 7, which is:

2-chlorobenzenesulfonic acid 3-[(3-amidinophenyl)methoxy]-5-methylphenyl ester hydrochloride;

2-chlorobenzenesulfonic acid 3-[[3-(N-hydroxy)amidinophenyl]methoxy]-5-methylphenyl ester hydrochloride;

2-chlorobenzenesulfonic acid 3-[[3-(N-methylamidino)phenyl]methoxy]-5-methylphenyl ester hydrochloride;

2-chlorobenzenesulfonic acid 3-[(4-amidinophenyl)methoxy]-5-methylphenyl ester hydrochloride; or

2-chlorobenzenesulfonic acid 3-[(3-amidinophenyl)methoxy]phenyl ester hydrochloride.

13. A pharmaceutical composition for inhibiting proteolysis in a mammal, comprising an amount of a compound of any one of claims 1-12 effective to inhibit proteolysis.

14. The pharmaceutical composition of claim 13 further comprising a pharmaceutically acceptable carrier or diluent.

15. The pharmaceutical composition of claim 13, comprising an amount of a compound of any one of claims 1-12 effective to inhibit a trypsin-like protease.

16. A method of inhibiting proteolysis in a mammal, comprising administering to the mammal a composition of claim 13.

17. The method of claim 16, wherein a trypsin-like protease is inhibited.

18. A method of treating pancreatitis, thrombosis, ischemia, stroke, restenosis, emphysema or inflammation in a mammal, comprising administering to the mammal a composition of claim 13.

19. A method of inhibiting thrombin-induced platelet aggregation and clotting of fibrinogen in plasma, comprising administering to the mammal a composition of claim 13.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/20087

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 38/05
US CL :514/19
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/19; 562/445, 562/560

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, CAS Online

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, A, 4,316,889 (BAJUSZ et al.) 23 February 1982, see entire document.	1-14, 16-19

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
07 APRIL 1997	24 APR 1997

Name and mailing address of the ISA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	DAVID LUKTON
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/20087

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 15
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.